Palladium catalysis supported on glass beads

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PALLADIUM CATALYSIS SUPPORTED ON GLASS BEADS

submitted by Louise Tonks

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Abstract

This thesis describes a novel type of palladium catalysis using glass bead technology.

Chapter 1 reviews the literature, discussing the merits of homogeneous and heterogeneous catalysis with water-soluble catalysts. This leads into the use of supported aqueous phase catalysis (SAPC) for various transition metal catalysed reactions.

Chapter 2 describes the optimisation of a supported aqueous phase palladium-catalyst (with trisulfonated triphenylphosphine (TPPTS) as the water-soluble ligand) and the various types of glass bead complexes that have been synthesised. The Heck reaction was studied in depth using the bead complexes with various substrates. All reactions were compared with the homogeneous system in terms of reaction time, yield and palladium leaching into the product.

Chapter 3 extends the methodology used in Chapter 2 towards applications in other palladium catalysed reactions. The reactions chosen for study include allylic substitution, Suzuki couplings and allylic rearrangements. Again the various bead complex preparations were implemented, their activity noted and compared to the traditional homogeneous system. The use of the palladium based SAPC in the allylic rearrangement proved problematic.

Chapter 4 leads on from the failing reactions in Chapter 3, namely the allylic rearrangement reaction. In an attempt to improve the homogeneous reaction, by removing the metal contamination from the final product, we designed novel 'sponge beads'. These 'sponge beads' were tested in various homogeneous palladium-catalysed reactions and were compared with other filters. Further optimisation of the preparation of the 'sponge beads' gave an estimate of quantities required for any scale reaction. Other miscellaneous tests were performed in this section with the aim of confirming assumptions made throughout the research performed.

Keywords: palladium, catalysis, glass beads, TPPTS, SAPC, 'sponge beads'.

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Contents

Abbreviations

AA	atomic absorption
Ac	acetate
Ac_2O	acetic anhydride
acac	acetylacetonate
amphos (iodide)	2-diphenyl(phosphino)ethyl trimethylammonium iodide
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINAS	2,2'-*bis*(diphenylphosphino)methylene binaphthyl
Boc_2O	di-*tert*-butyl carbonate
Boc	*tert*-butoxycarbonyl
BSA	*N,O-bis*(trimethylsilyl)acetamide
t-Bu	*tert*-butyl
cat.	catalytic
(*S,S*)-chiraphos	(*S,S*)-2,3-*bis*(diphenylphosphino)butane
cm	centimetre
conv.	conversion
CPG	controlled-pore glass
(*S,S*)-cyclobutaneDIOP	(*S,S*)-1,2-*bis*((diphenylphosphino)methyl) cyclobutane
dba	*trans,trans*-dibenzylideneacetone
DIBAL-H	*di*-isobutylaluminium hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-*bis*(diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide

DMSO	dimethylsulphoxide
DVB	divinylbenzene
E^+	electrophile
e.e	enantiomeric excess
Et	ethyl
Et_2O	ether
g	gram
GC	gas chromatography
h	hour
HexDPPDS	hexyl-*bis*(sodium-*m*-sulfonatophenyl) phosphine
ICP	inductively coupled plasma
i-Pr	*iso*-propyl
IR	infrared
L	ligand
Me	methyl
min.	minute
mg	milligram
ml	millilitre
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance
NORBOS	3,4-dimethyl-2,5,6-*tris*(*p* -sulfonatophenyl)-1 -phosphanorborna-2,5-diene
Nuc	nucleophile
PEG	poly(ethylene)glycol
Ph	phenyl
phosphazene base	*tert*-butylimino -*tri*(pyrrolidino)phosphorane
(*R*)-prophos	(*R*)-1,2-*bis*(diphenylphosphino)propane
r.t.	room temperature
SAP	supported aqueous phase
SAPC	supported aqueous phase catalysis

skewphos (BDPP)	2,4-*bis*(diphenylphosphino)pentane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
TPP	triphenylphosphine
TPPMS	monosulfonated triphenylphosphine
TPPTS	trisulfonated triphenylphosphine

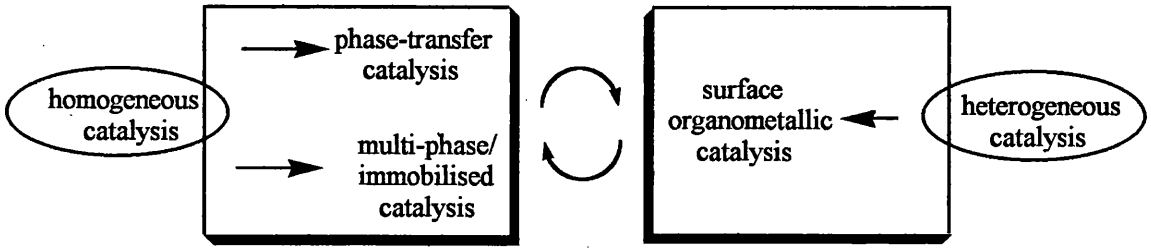
CHAPTER 1

INTRODUCTION

1.1 Introduction

For any catalytic process it is desirable that a catalyst should possess high activity/catalytic turnover concomitant with high regio- and stereoselectivity. These essential properties have emerged from the evolution of homogeneous transition metal catalysis over several decades. Despite such advancements, homogeneous catalysts have been under-used by the fine chemical industry, partly due to the problematic separation of catalyst and product. This is particularly necessary and required by legislation for compounds to be used in drug fabrication or for human consumption. Chemical industries need to drive towards producing clean, low temperature, low pressure and economical processes. Thus, rapid developments in the field of catalysis are leading to an increased demand for tailor-made catalysts.[1]

In order to avoid the separation step, efforts have been made to immobilise homogeneous catalysts upon suitable porous carriers (**Scheme 1**). Solid supports such as polymers have been applied to many organic reactions and have been shown to be effective. Water-soluble complex catalysts are also being investigated intensively at the present time and have found wide applicability. The aim is to maintain the activity and selectivity of the homogeneous system whilst avoiding or minimising the leaching of the catalyst into the product. The advantages of a successful process would enhance economic potential whilst reducing possible toxicity from transition metals in a synthetic procedure.[2]



Scheme 1

More recently, the inherent advantages of both a water-soluble catalyst and an immobilised solid support were amalgamated to bridge the gap between homogeneous and heterogeneous catalysis to form what is termed a supported aqueous phase catalyst (SAPC). All the areas above will be discussed in turn to illustrate the impetus for work on palladium-based SAPC.

1.2 Homogeneous catalysis

The unbeatable advantage of organometallic chemistry is its clear, normally well-defined molecular structure combined with structural variability.[3] The main shortcoming of homogeneous catalysis is the need for separating the catalytic species from reaction products at the end of the reaction. In many cases this is not a problem. However, if the catalytic species is expensive, e.g. rhodium phosphine complexes, then a very effective separation is required. With pharmaceuticals, there is the additional constraint of minimising catalyst contamination of the products because of their toxicity.

A vast array of selective chemical transformations can now be facilitated by homogeneous transition metal catalysis both in organic and aqueous media.[4] Therefore, there continues to be a need for successfully immobilising (*heterogenising*) transition metal catalysts to enhance the economic potential and decrease possible toxicity hazards of transition-metal-mediated catalytic conversions.

In principle, immobilisation may be achieved by several methods such as physical adsorption or chemisorption of a metal complex onto a support; entrapment of metal complexes *via in situ* synthesis within zeolites; dissolution of a metal complex in a non-volatile solvent or dissolution of a metal complex in a non-volatile solvent that is adsorbed onto the surface of a support, i.e. supported liquid phase (SLP). In general, the immobilised systems never approach the combined activity/selectivity performance levels of their homogeneous counterparts and tend not to retain the metal complexes for long enough.[5]

The strengths and weaknesses of homogeneous and heterogeneous catalysis are summarised in **Table 1** below.

Table 1. Advantages and disadvantages of homogeneous and heterogeneous catalysis

	Homogeneous catalysis	Heterogeneous catalysis
Activity (relative to metal content)	high	variable
Selectivity	high	variable
Reaction conditions	mild	harsh
Catalyst recycling	expensive	not necessary
Service life of catalyst	variable	long
Variability of steric and electronic properties of catalysts	possible	not possible
Mechanistic understanding	plausible under random conditions	more or less impossible (except for model systems)
Sensitivity toward catalyst poisons	low	high

1.3 Water-soluble catalysts

The use of water-soluble ligands as part of the catalyst complex in reactions is a rapidly expanding area for study. A flavour of the type of ligands synthesised and their applications in reactions will be discussed to illustrate the beneficial qualities they possess. The idea is to provide an overall picture of the different types of water-soluble catalyst systems which have evolved recently and the use of the sulfonated ligands in our research, namely TPPMS and TPPTS. For a more detailed study on some examples of palladium-catalysed reactions using the above mentioned water-soluble ligands see Chapters 2 and 3.

As previously mentioned, the problem of a homogeneously catalysed processes lies in the separation of the product phase from the soluble (molecular) catalyst. The processes necessary to achieve this usually includes thermal operations such as distillation, decomposition, transformation, and rectification, which usually lead to thermal stress on the catalyst. These can cause decomposition reactions and progressive deactivation during the lifetime of the catalyst. Furthermore, thermal separation processes seldom give quantitative recovery of the catalyst, which causes loss of productivity through loss of metal.

1.3.1 Biphasic reactions

The solvent themselves can cause environmental problems if they are released to air, land or water. Hence, a movement towards environmentally benign solvents e.g. water is desirable. The solvent (water) does not usually act as an inert diluent but rather plays an active role in catalysis. Product separation is simpler for two-phase systems (biphasic) incorporating water-soluble catalysts. The hydrophilic catalyst, which is insoluble in the organic product phase, is a (organometallic) coordination complex, and as such is molecularly well defined as with conventional homogeneous catalysts (**Figure 1**). The catalytic reactions (e.g. C-C coupling) occur in the aqueous phase or at the phase boundary, and the catalyst is removed from the product at the end of the reaction by a simple phase separation. Thus, the separation processes which could have a detrimental effect on the active life of the catalyst, are thereby avoided.

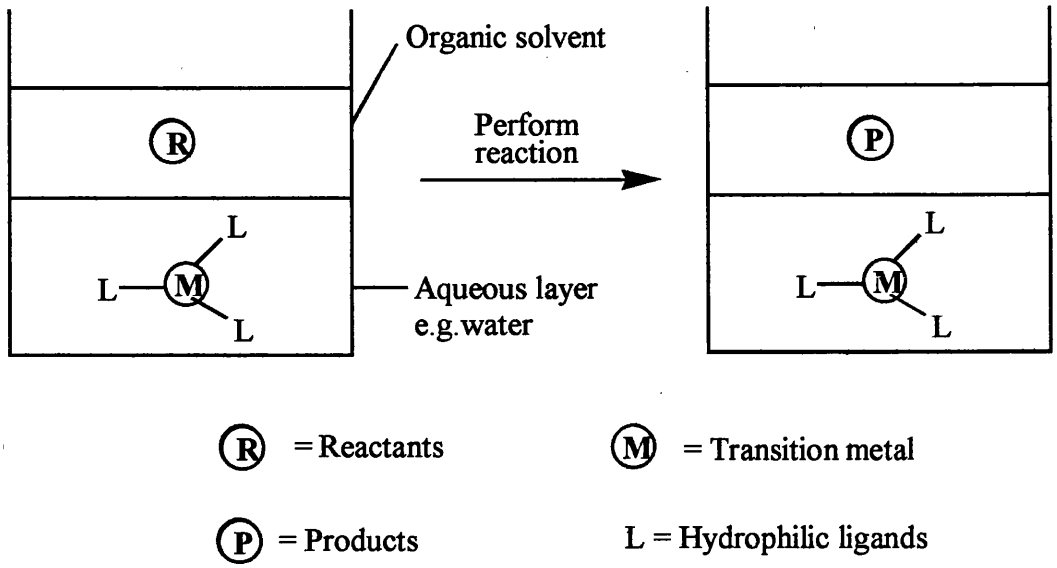
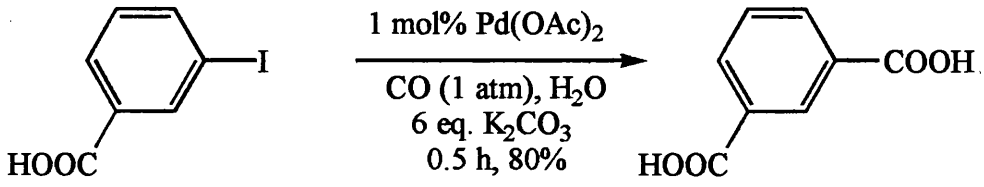


Figure 1

Other advantages of using water-soluble catalysts includes the use of water as solvent and mild reaction conditions which provides an environmentally friendly protocol, and the ability to recycle the catalyst without any depreciable loss of catalytic activity. The water-soluble catalysts also seem to show similar activity and selectivity to the homogeneous system.

Beletskaya *et al* demonstrated palladium catalysed carbonylation reactions both in organic[6] and aqueous media.[7] Applying the latter solvent system they prepared the aromatic acid **2** from the aryl iodide **1** at room temperature under 1 atm of CO in a mixed solvent of H_2O/DMF (1/1 or 1/2, v/v), or in water alone (in the case below) depending on the solubility of the substrate.[8] The "ligandless" palladium(II) complex, $Pd(OAc)_2$, was used as the precursor of the catalyst, using K_2CO_3 as the base.



1 **2**

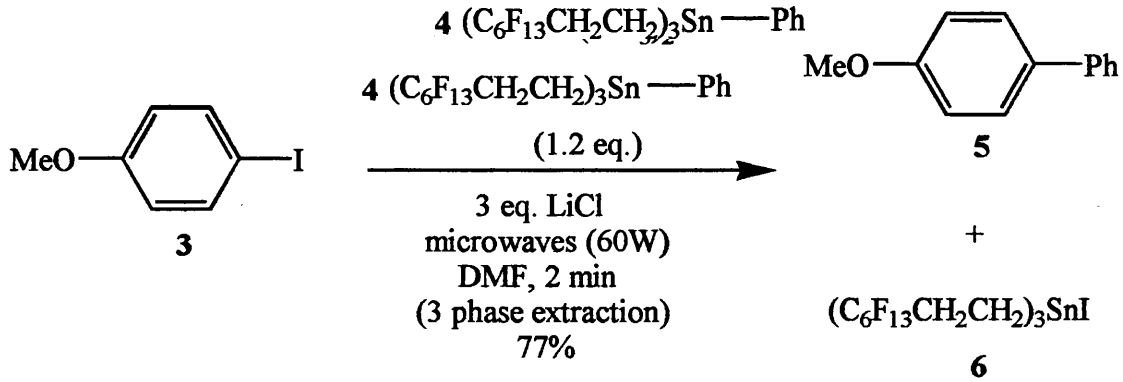
However, one apparent problem lies with separation of catalyst from product when water-soluble products are synthesised. One alternative to overcome this predicament is to use a solvent which does not interfere with these products such as a fluorous source.

2 mol% $Pd(PPh_3)_2$

1.3.2 Alternative biphasic system

Fluorous biphasic systems are a novel method for easing separation of the catalyst or reagent from the product under mild conditions, preventing metal leaching into the organic layer, that can be applied to *water-sensitive* chemical reactions (hence they are favoured over normal biphasic systems). This is a rapidly expanding area developed by Horváth[9] and Rábai at Exxon and many examples of fluorous ligands[10] are being pursued. The application of this new technique has been performed in various reactions such as hydroboration,[11] oxidations[12] and Stille couplings.[13]

The latter reaction took place in a conventional organic solvent under microwave irradiation using a two-phase mixture consisting of the fluorous tin reagent **4** and the aryl iodide **3** and in only two minutes the biaryl **5** was formed. Three phase extraction (aqueous, dichloromethane and perfluoroheptanes) facilitated work up and removal of tin residue **6**.



1.3.3 Classes of water-soluble phosphines

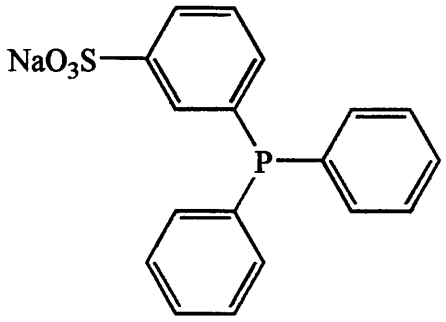
Numerous complexes with the metal in a low oxidation state are stabilised by phosphorus-containing ligands. Therefore much work has been carried out to tailor these ligands with appropriate polar substituents, including carboxylic, amino, hydroxy, and sulfonate functions, which induce solubilisation in water.

a) Sulfonated phosphines

It was believed that the best hydrophilic substitute for triphenylphosphine (TPP) as a ligand for a water-soluble complex catalyst would be the sodium salt of an appropriate TPP sulfonate, which is thermally stable.[14]

Sulfonated phosphines at present constitute the most widely used class of ligands in water-soluble metal complexes, especially in catalysis. The investigation of the catalytic properties of transition metal-sulfonated triphenylphosphine complexes began in 1972. It soon became apparent that this phosphine was capable of stabilising the lower oxidation states of many transition metal ions in aqueous solution.[15]

The two most frequently used water-soluble phosphines for catalytic application are the mono- and trisulfonated triphenylphosphines, TPPMS (**7**) and TPPTS (**8**), respectively.[1,16]



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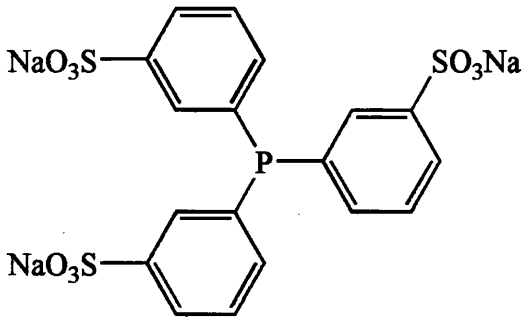

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Several features of water-soluble ligands (such as TPPTS) are important when they are being considered for use in the synthesis of homogeneous catalysts. One factor is that the cone angle of TPPTS (170°) is larger than that of triphenylphosphine (145°) according to Tolman,[17] which results in the formation of complexes having lower coordination numbers.[18]

TPPMS complexes

Transition-metal compexes of TPPMS have been used as catalysts for hydrogenation, hydroformylation, and carbonylation reactions. The complex $PdCl_2(TPPMS)_2$ has been used as a two-phase aqueous-organic catalyst for the carbonylation of allylic chlorides[19] and the reaction proceeds smoothly under 1 atm pressure of carbon monoxide. A similar reaction of allyl chlorides and acetates with sodium formate (acting as a hydride donor) is also catalysed by $PdCl_2(TPPMS)_2$.[20] In this system, the water-soluble complex transports the substrate into the aqueous phase and causes it to be reduced by sodium formate. The product is a mixture of the 1- and 2-alkene.

According to experiences of Wilkinson and Jóo, monosulfonated triphenylphosphine (with a carbon/sulfonate ratio of 18) would be slightly foamy, extractable and thus too lipophilic (or hydrophobic) for use in aqueous reactions.[21] Therefore it proved essential to use the non-detergent, highly water-soluble (and thus hydrophilic) trisulfonated triphenylphosphine (carbon/sulfonate ratio of 6) which was not extracted by an organic medium.

TPPTS complexes

More extensive use has been made of TPPTS than of TPPMS as a ligand for preparing water-soluble homogeneous catalysts. The major reason for this is that the presence of the three sulfonate groups on TPPTS enables it to have a greater solubility in aqueous solution than does TPPMS.

i) Hydroformylation

The principle application of TPPTS has been as a ligand for rhodium in catalyzed hydroformylation reactions. In the hydroformylation of propene with such catalyst systems, the reaction conditions use an equimolar mixture of carbon monoxide and hydrogen at 40 bar pressure and 125 °C in an aqueous solution of pH 6.0 (**Figure 2**).[22] The two phases are decanted quickly and cleanly and the product was separated easily from the aqueous phase without significant catalytic loss. Any propene whose solubility in butanal decreases sharply above its critical point (91 °C) is recycled at counter flow with the $CO\text{-}H_2$ stream. In the reactor, the yield of *n*-butanal and *iso*butanal/propene is 99% (<90% for the conventional cobalt process).

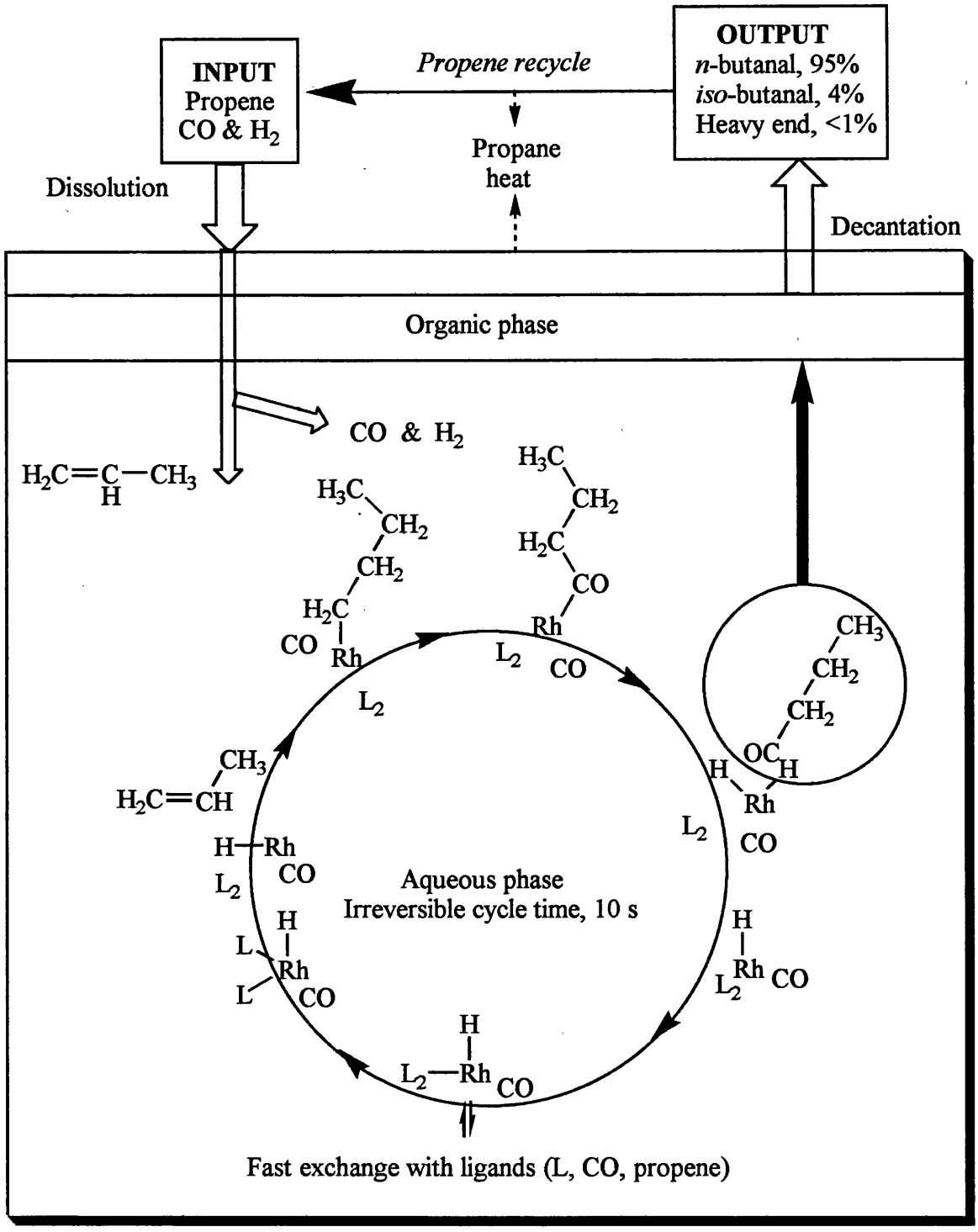
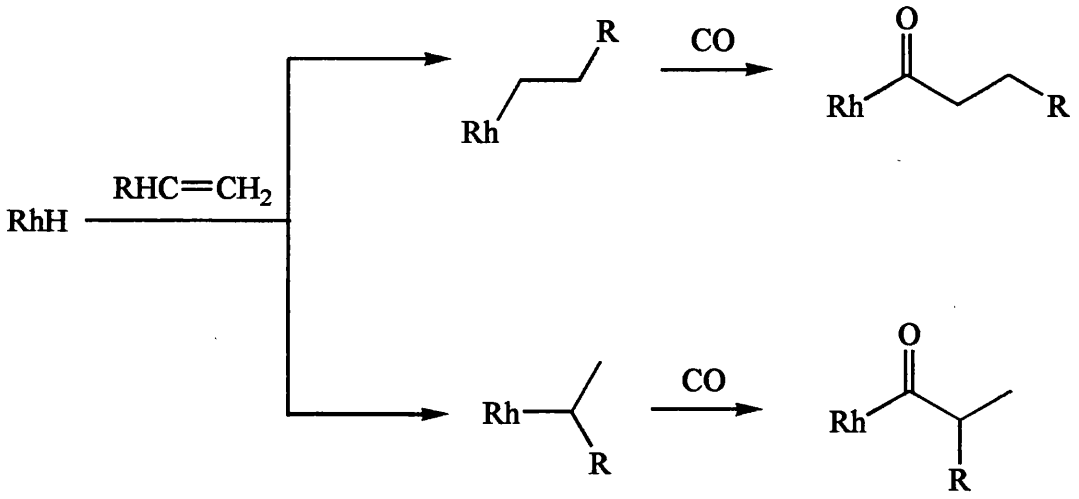


Figure 2: Probable catalytic cycle in the biphasic system: At 125 °C, the three gases dissolve in the aqueous phase and react with the rhodium complex, to generate a butanal molecule. The butanal molecule is decanted off and removed from the reaction mixture. L, water-soluble ligand TPPTS.

Excess ligand stabilizes the system against decomposition. By comparison, this catalyst system is less susceptible to poisoning than its rhodium triphenylphosphine analog. With the aqueous-based process, the problem of hydroformylating large olefins is no longer the removal of the product but the solubility of the substrate.

A comparison of homogeneous rhodium hydroformylation catalysts having either TPPTS or PPh_3 as supporting ligands shows that the hydrophilic TPPTS gives higher linear : branched isomer ratios but lower overall activities than does PPh_3. The linear : branched isomer ratio reflects the amount of linear : branched alkyl and acyl complexes that is formed in the insertion steps (**Scheme 2**).



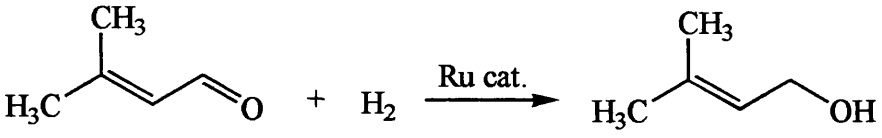
Scheme 2

Higher steric requirements favour the linear isomer. The greater cone angle for TPPTS *may* be the cause of higher linear : branched ratios being found for the TPPTS rhodium hydoformylation system.

ii) Hydrogenation

Water-soluble phosphine complexes of the late transition metals can be used as catalysts for the hydrogenation of C=C and C=O double bonds. Thus the complex $RhCl(TPPTS)_2$ is an effective catalyst in aqueous solution for the hydrogenation of alkenes. Complexes containing two phosphines per catalyst molecule were found to be more active than those with three phosphine ligands.[15] A problem with using this complex is that TPPTS ligand is oxidised more readily than PPh_3 in $RhCl(PPh_3)_3$.

This situation occurs as Rh(III) complexes catalyse oxygen transfer from water to TPPTS to give the oxide (TPPTS=O). However, Rh(I) and Ru(II) complexes can be used for hydrogenation, such as the selective reduction of α,β-unsaturated aldehydes to unsaturated alcohols.[23] A catalyst formed from $RuCl_3$/TPPTS reduces 3-methyl-2-butenal **9** to 3-methyl-2-buten-1-ol ("prenol") **10** with 96% selectivity and excellent conversion.



9 **10**

Joó *et al* have reported use of the ubiquitous TPPTS in combination with either Rh[24] or more recently Ru[25] to catalyse the hydrogenation reactions, and with the latter transition metal found that the pH of the reaction solution was crucial for effective hydrogenation of unsaturated aldehydes.

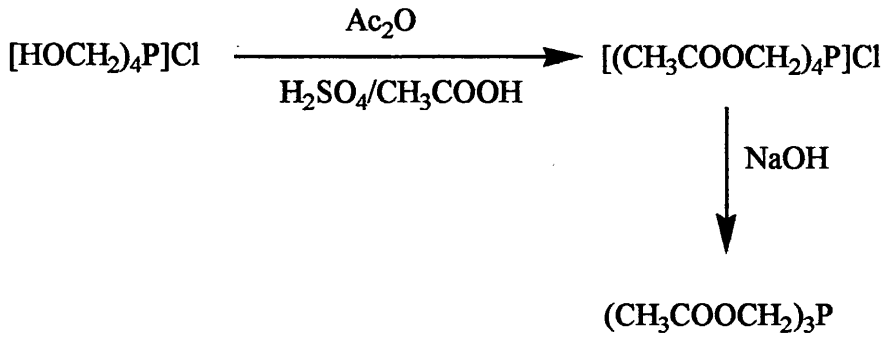
Blart *et al* demonstrated new synthetic applications for a water-soluble palladium acetate/TPPTS catalyst generated *in situ*.[26] They applied their catalyst to diyne synthesis and intramolecular cyclisations. Variations on the sulfonated ligands have also been prepared, namely potassium salts of trisulfonated triphenylphosphine[27] and diazosulfonates ("diazo-TPPTS").[28]

Metal complexes of TPPMS and TPPTS have amphiphilic character because of the presence of both hydrophilic sulfonate groups, and hydrophobic phenyl groups in the ligand structure. This feature allows the complex to transfer readily between the aqueous and organic phases in a biphasic system. Furthermore, these complexes can aggregate to form micelles, or surface-active compounds. This property may be particularly important when the properties and selectivities of catalysts formed by such phosphines are being considered.

b) Carboxylated phosphines

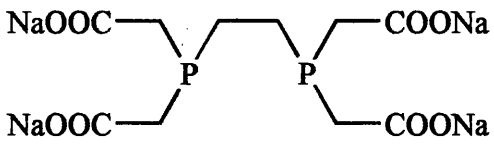
Phosphanes with carboxylic groups were some of the earliest investigated water-soluble phosphanes. Condensation of a phosphido salt with an ω-haloester or ω-halocarboxylate leads to the corresponding ω-phosphinoesters or acids.[29] Similarly, secondary phosphines react directly with ω-bromoesters to yield the ω-phosphinoesters.[30]

An indirect procedure has been used to prepare the tris(acetoxymethyl) phosphine ligand by acetylation of tetrakis (hydroxymethyl) phosphonium chloride with acetic anhydride, followed by cleavage with sodium hydroxide, according to **Scheme 3** below:[31]



Scheme 3

One of the most important examples is the phosphane analog of ethylenediaminetetraacetic acid. It is obtained as the air-stable monohydrate of the tetrasodium salt (**11**). The carboxylated ligands are only soluble in basic media.



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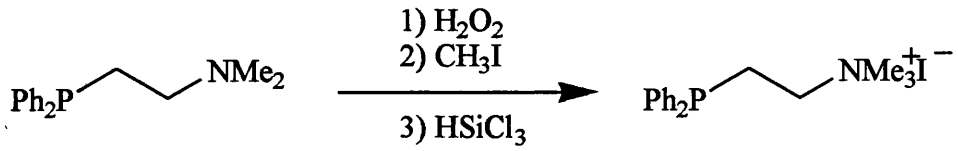
c) Aminated phosphines

Phosphines for which solubility in water is achieved by quarternary amines as functional groups are also of interest. They are generally obtained through the synthesis of nitrogen-containing phosphine ligands followed by quaternisation.[31] According to the general preparative procedure for tertiary aminophosphines,[32] chlorophosphines and phosphides are essential precursors.

Before the nitrogen atom can be alkylated, the (more reactive) phosphorus centre has to be protected, either by oxidation or by coordination to a metal (**Scheme 4**). Subsequent reduction or decomplexation, respectively, yields the desired phosphane ligands. The most important example of this class of substances is "amphos" (**12**), first synthesised by Baird *et al.*[33] However, ligands of this type contain amino groups which are only soluble in acidic media.



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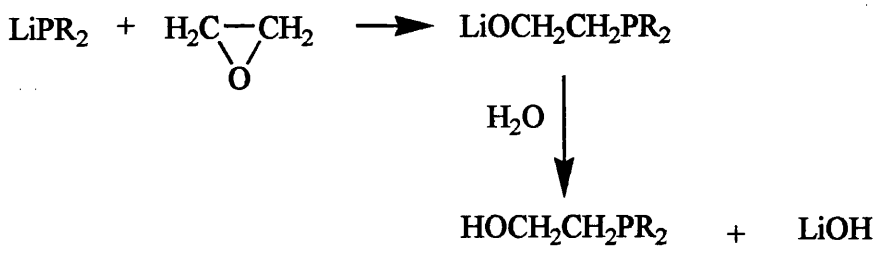
Scheme 4

The "amphos" ligand has been complexed to rhodium with hydride, olefin and carbon monoxide ligands and utilised as olefin hydrogenation and hydroformylation catalysts in aqueous solution and in two-phase systems.[34] Virtually no leaching (<0.1% of total rhodium used in reaction) of metal was detected in the organic layer in the two-phase system. Baird and Markiewicz synthesised a cobalt carbonyl complex using "amphos" as catalyst for use in olefin hydroformylation reactions, but it proved less effective than the analogous rhodium system.[35]

d) Phosphines involving alcohol or ether as a functional group

Condensation of a primary or secondary alkyl- or arylphosphine with ketones or aldehydes in the presence of hydrochloric acid affords hydroxyalkylphosphines by repeated addition of a carbocation to the phosphine, followed by elimination of HCl from the phosphonium salt being formed.[36]

Addition of a phosphide salt to an oxirane, or more generally to a cyclic ether, provides, after hydrolysis, the corresponding hydroxyalkylphosphine **13**, as shown in **Scheme 5**.[37]



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Scheme 5

e) Other water-soluble phosphines

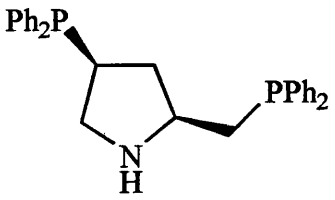
Various other water-soluble phosphines have been synthesised and used in aqueous or biphasic systems for use in hydroformylation[38] and hydrogenation reactions.[39] Two independent groups have reported use of maleic anhydride or a maleic anhydride phosphine as starting material to synthesise bicyclic[40] and bidentate[41] ligands respectively, which were thought to have potential for use in hydrogenation and hydroformylation reactions.

Other groups have synthesised novel amphiphilic diphosphines which were combined with a rhodium catalyst to ensure complexation, the complex was then employed in hydroformylation reactions with success.[42,43] Various phosphanorbornadienephosphonates[44,45] have been synthesised as water-soluble phosphines for biphasic hydroformylation reactions (based on knowledge that NORBOS shows outstanding activity in such hydroformylation reactions with propene). Knight *et al* prepared triphenylphosphine monophosphonates to make platinum(II) complexes.[46]

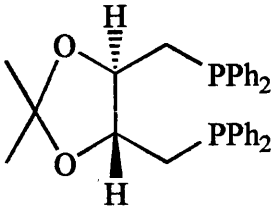
f) Enantiomerically pure ligands

A number of water-soluble enantiomerically pure phosphine ligands have been identified as reagents for catalytic asymmetric induction. Most of them contain sulfonated groups. The two main preparative routes require either the introduction of a polar functional group into an enantiomerically enriched diphosphine or the binding of a enantiomerically pure moiety to a diphosphine ligand.[47] Most studies have been carried out on 2-(diphenylphosphinomethyl)-4-(diphenylphosphino)pyrrolidine **14** and 2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane **15** (DIOP).

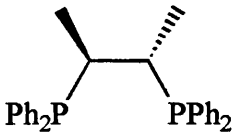
Other ligands have also been used such as (*S,S*)-chiraphos **16**, (*R*)-prophos **17**, skewphos **18** and (*S,S*)- cyclobutanediop **19**:-



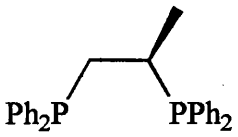
14



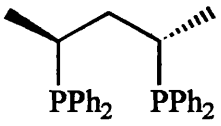
DIOP **15**



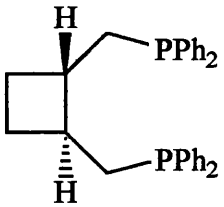
chiraphos **16**



prophos **17**



skewphos **18**



cyclobutanediop **19**

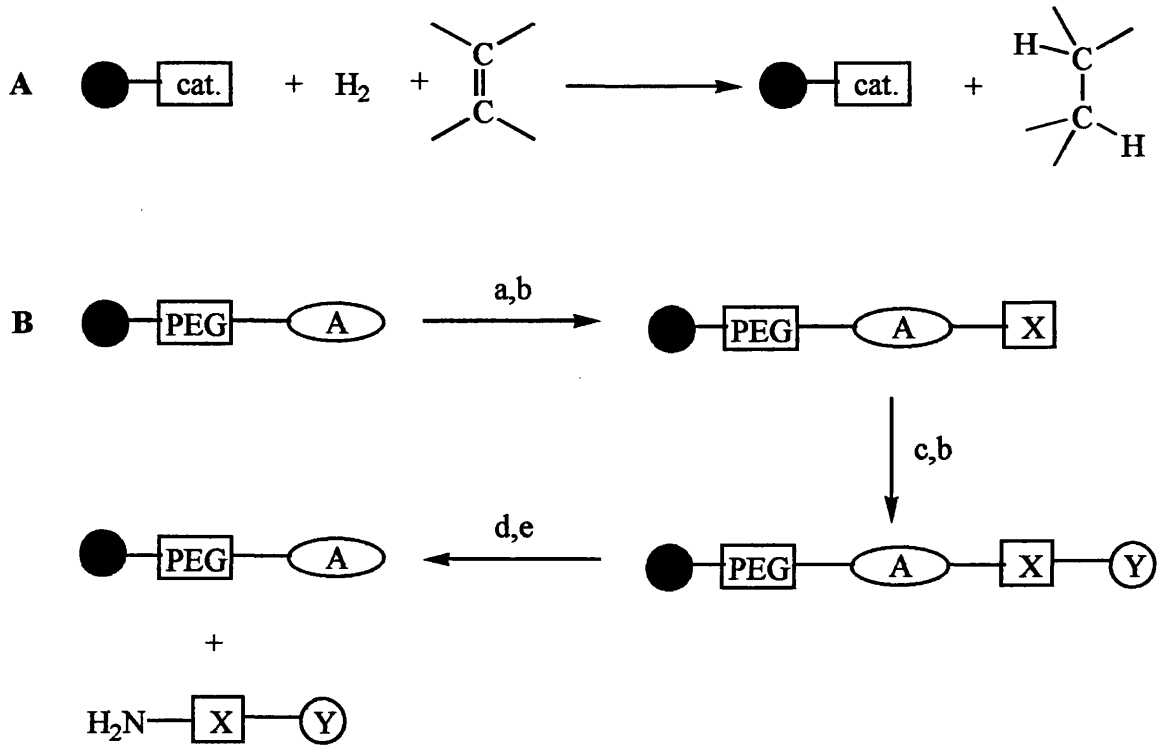
These enantiomerically pure ligands have been derivatised by the introduction of polar groups for use in aqueous or biphasic asymmetric catalysis reactions. Water-soluble enantiomerically enriched ligands have been synthesised[48] and employed in hydrogenation[49] and hydroformylation[50] reactions to give good enantioselectivities. Enantiomerically pure water-soluble phosphine ligands were found to be useful in other reduction reactions. For example, hexa-sulfonated 2,2'-bis diphenylphosphinomethylene binaphthyl (BINAS) was used for the reduction of nitro compounds to amines[51] and a novel ligand based on a water-soluble acrylic acid-rhodium cationic complex was employed in asymmetric hydrogenation reactions to give reasonable enantioselectivities.[52]

Although biphasic reactions have proved to be successful in some cases, these reactions are impeded by solubility of substrates in the aqueous layer in which the catalyst resides and a limited interface between the reactants, although this technique does allow for the opportunity for rational catalyst design and optimisation.

1.4 Heterogeneous catalysis

1.4.1 Immobilisation using solid supports

Tailor-made catalytic supports is an obstensibly rich yet little explored field. The huge current interest in solid-phase organic synthesis can be largely attributed to the development of combinatorial chemistry. There is frequent reporting of work in the area and there is much potential for further expansion within the field.[53] Only recently the advantages of support-bound reagents and the opportunities offered by solid-phase catalysis have been recognised. These solid supports either attach directly to the substrate under study **(Scheme 6B)** or bind to a catalyst **(Scheme 6A)**.

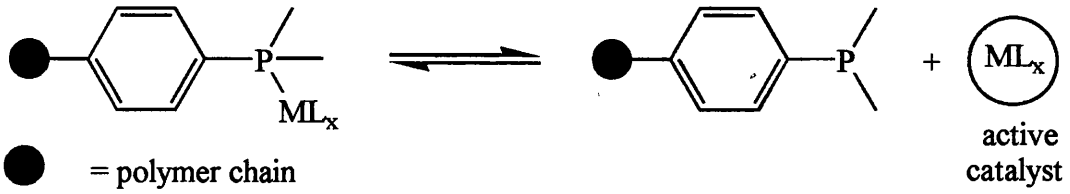


Scheme 6: Schematic representation of **A)** a one-step reaction with a polymer-supported reagent, a covalently bound hydrogenation catalyst. **B)** Schematic representation of a reaction with a polymer-supported substrate bound by a support-linker (PEG)-anchor (A) combination. a) Coupling of compound X to the support; b) removal of excess reagents; c) derivatisation of X with Y; d) reduction of the anchor; e) cleavage of the final product.

Use of solid-phase in synthesis offers many advantages over the homogeneous system such as simplified reaction procedures (removal of time-consuming purification and isolation steps) which involves removal of the product from the solid support by simple filtration and washing; solid supports use an excess of reagents to drive a reaction to completion and often higher yields can be obtained, however, careful reaction conditions must be applied to avoid side reactions; possibility of recovery of the support and re-use if appropriate cleavage conditions and suitable anchor groups are chosen; and applications of solid supports in automation process to name but a few. However, these supports also have some limitations: they can be expensive to prepare, their stability under certain reaction conditions, such as in very strongly acidic or basic media, may be poor, and side reactions with a polymer itself may occur during the course of a reaction.[54]

Solid supports attached to a catalyst

The catalyst could be immobilised on a solid support by absorption onto a permeable solid such as montmorillonite or by attachment to a polymer such as macroreticular polystyrene. Catalyst recycling is free from problems in heterogeneous catalysis as the catalyst metal either remains in the solid bed of the reactor after reaction or can be recovered readily from a catalyst suspension by filtration or centrifugation with subsequent recycling. A technique practiced for a long time without any spectacular success is to immobilise solid complex catalysts on such solid (stationary) supports. Here, the continuous loss of the metal (bleeding or leaching) or the catalyst being so tightly bound that the reaction rate is too slow are serious disadvantages.[3] Leaching normally results from the dissociation of the metal from one of the anchored ligands (**Scheme 7**), thus liberating the (active) molecular catalyst.

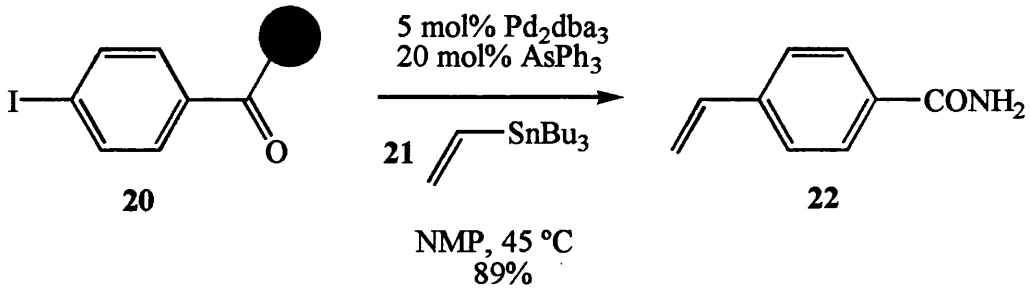


Scheme 7

Leaching can also originate from structural changes with concomitant weakening of certain bonds during the catalytic cycle, during which the coordination sphere of the metal undergoes continuous change. Thus, specific bonding type between catalyst and support is essential. However, immobilisation of a catalyst in a mobile phase, that is, an aqueous solution immiscible with the product phase, represents an almost ideal combination of homogeneous and heterogenous reaction processes.

Solid supports attached to substrates

Many solid-phase syntheses have been performed on everyday palladium-catalysed reactions such as the Heck, Suzuki, allylic substitution (which will be discussed in Chapters 2 and 3) and Stille couplings.[55] In one instance immobilised 4-iodobenzoic acid was used to investigate the Stille reaction.[56] The reaction of iodobenzoic acid **20** with the vinylstannane **21** in the presence of palladium and $AsPh_3$ overnight generated the substituted arene **22** in good yield, based on the loading of iodobenzoic acid on the resin. The product was cleaved from the resin with 5% TFA/CH_2Cl_2.



Use of solid supports in various organic syntheses are regularly reported in the literature. Polymers have been effectively used in key reactions such as the Sharpless asymmetric dihydroxylation[57] where the polymer was tethered to the substrates or the polymer was introduced as an integral part of the perruthenate reagent in mild oxidation reactions.[58] Both examples show potential applicability for automated synthesis to produce chemical libraries.

Silica supported catalysts

Angelici and Gao reported a combination catalyst that consisted of a homogeneous catalyst tethered to a silica-supported palladium heterogeneous catalyst in arene hydrogenation experiments.[59] They assumed the combination catalysts, consisting of a tethered complex on a supported metal (TCSM) catalyst, could function by synergistic action of both catalyst components (**Figure 3**). They hypothesised that for the hydrogenation reaction of unsaturated organic substrates, the H_2 would become activated on the supported metal (e.g. Pd, Rh, or Pt) with the resulting hydrogen atoms spilling over onto the silica where they could react with the unsaturated organic substrate that is simultaneously coordinated and activated by the tethered complex.

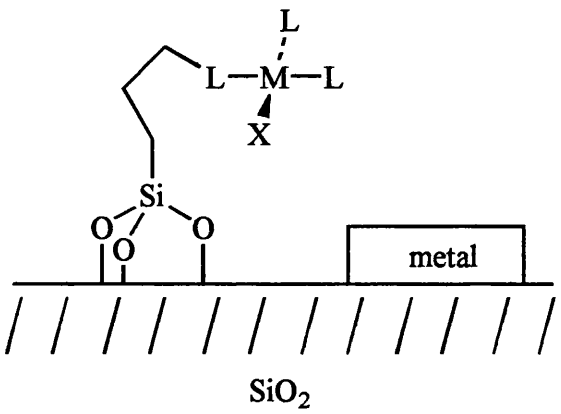


Figure 3

They found that the activity in the hydrogenation of arenes was much higher with the TCSM system that that of the tethered complex or the supported metal separately. The activity was much better than the homogeneous or immobilised metal complex system under the mild conditions of 1 atm of H_2 and 40 °C.

Huang *et al* have reported silica-supported palladium complexes for use as the catalyst in butoxycarbonylation[60] and carbonyl allylation[61] reactions and found they were easy to handle, separate the products and re-use the catalyst with success. In some cases higher catalytic activity was obtained compared with the traditional homogeneous system. Many other silica related supports have been developed such as mesoporous materials, but these will not be discussed.

Much effort has been implemented in the hope to harness the power of transition metal catalysis by anchoring ligands to various supports, but the efficacy of modified catalysts is often hampered by the suppression of catalyst mobility stemming from the anchoring process.[62]

1.5 Supported Aqueous Phase Catalysts

One innovative answer to this problem, which seems to offer the ideal union of the chemical advantages of homogeneous catalysis (defined species of catalyst, gentle reaction conditions, high activity and selectivity) with the practicability of a solid, heterogeneous system (e.g. long lifetime, easy separation between product and catalyst), is supported aqueous phase catalysis (SAPC). This is considered to be an elegant way of heterogenising biphasic catalysts.[63] It was first demonstrated in 1989 when *Davis et al* showed that very hydrophobic alkenes such as oleyl alcohol, octene, or dicyclopentadiene could be hydroformylated successfully with the water-soluble catalyst $[HRh(CO)(TPPTS)_3]$.[5]

This technique uses the hydrophilic nature of the surface of controlled pore glasses (CPG)[64] to adhere a polar solvent layer (such as water or ethylene glycol) in which a hydrophilic catalyst can be anchored. Thus, the catalyst is dispersed over a large surface area (surface area 1 g of CPG 240Å = 77.5 m^2) and the catalyst retains mobility within the polar solvent on the bead. In contrast to many other supports the beads are stable to mechanical and thermal fatigue.[12]

The concept of SAPC stemmed from supported liquid phase catalysis (SLPC), a technique in which a catalyst is deposited on the surface of a high surface area porous inorganic oxide in a thin film of a non-volatile solvent; reactants and products are in the gas phase. However, this approach is limited to gaseous reactants. Glass bead technology and related methods have shown wide applicability in various transition metal catalysed reactions.

1.5.1 Preparation of the SAP Catalysts

These catalysts consist of a thin film that resides on a high surface area hydrophilic support, such as controlled-pore glasses or silica, and is composed of an aqueous solution of organometallic complexes as illustrated in **Figure 4**.

Reactions of liquid-phase, water-insoluble organic reactants take place at the film-organic interface. This point is critical since it eliminates the need for water-soluble reactants.

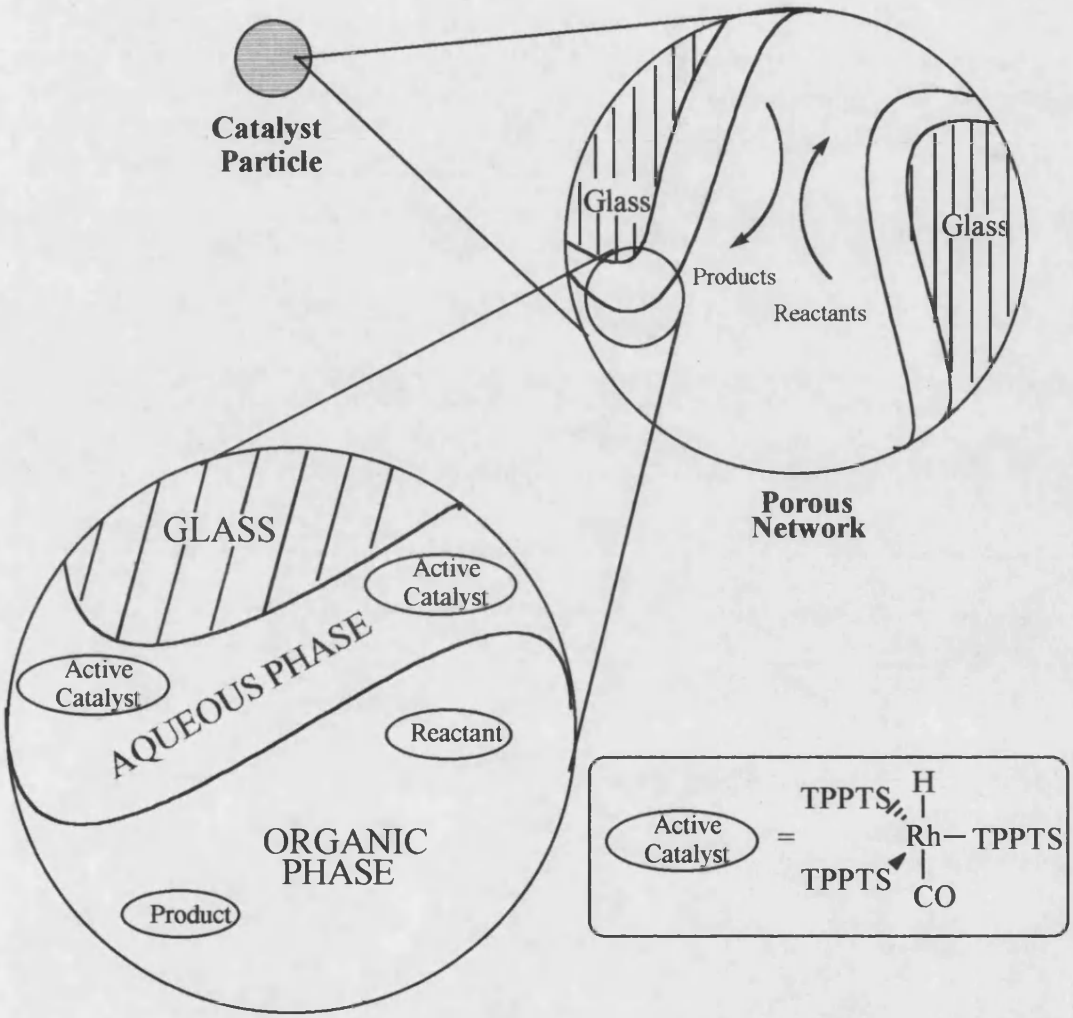


Figure 4

The key is imparting water solubility to an organometallic complex that is known to be a homogenous catalyst in organic media by modifying the water-solubility of its ligands. The water-soluble complex is supported on a hydrophilic solid to create a large interfacial area between the catalytic species and the organic reactants. The hydrophilicity of the ligands and the support creates interaction energies sufficient to maintain the immobilisation.

To produce a typical SAP catalyst, a granulated, porous support material with a large inner surface area is added to a stirred aqueous solution of $[HRh(CO)(TPPTS)_3]$ and TPPTS (ligand excess), and then dried under vacuum. The hydrophilic carriers consist of "controlled pore glass" (CPG) with a definite but variable large inner surface.

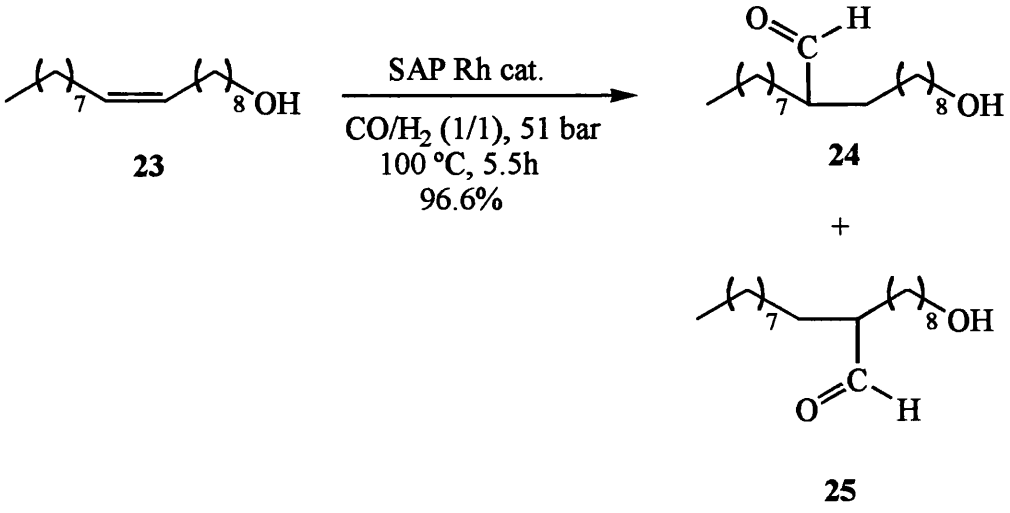
After removal of the solvent a dry, yellow powder remains which still contains about 2.9 wt % water. The metal complex is homogeneously distributed on the inner and outer surface of the support.

These SAP catalysts have been successfully tested for reactions such as hydroformylation of heavy[65] or functionalised olefins,[66] selective hydrogenation of α,β-unsaturated aldehydes,[67] asymmetric hydrogenation,[68] Suzuki couplings,[69] allylic substitution and Heck reactions.[70] Their main advantages concern easy catalyst recovery, increased activity (through a sharp increase of interfacial surface area on the silica support, a property particularly sensitive with sparingly water soluble reactants) and good selectivity (by conservation of the metal environment which is essential in asymmetric catalysis).

1.5.2 Hydroformylation reactions

The SAP catalysts were developed for the hydroformylation of liquid substrates that are completely insoluble in water, for example, oleyl alcohol.[71] As discussed above, one of the problems with converting from organic to aqueous solvents is the change in solubility of the catalyst complex. Like biological systems that function in water, e.g., vitamin B_{12} (Co), chlorophyll (Mg), haemoglobin (Fe), the organometallic catalysts contain ligands that ensure hydrophilic properties while the local environment at the metal remains hydrophobic in character.[63] Supported aqueous phase catalysts can be used to advantage in the hydroformylation reaction, since these catalytic reactions occur at the phase boundary, though characteristics such as water content can cause changes both in the reactivity and the linear : branched chain ratio of the product aldehyde.

Davis used the prepared SAP catalyst (as illustrated in **1.5.1**) and showed that oleyl alcohol **23** was hydroformylated into the C_{19} aldehydes **24** and **25** at 100 °C, 51 bar, and a CO/H_2 ratio of 1/1, in 96.6% yield without any rhodium loss at all. Moreover, after filtering off the stationary phase, the liquid phase did not contain rhodium, either as a complex species or as a colloid.



23 **24** + **25**

An alternative, self-assembly method of catalyst preparation involves loading $Rh(acac)(CO)_2$ onto the bead and then treating with a solution of water-soluble phosphine.[72] Ligand exchange in this case proved to be rapid as indicated by the colour change from white to yellow. This approach was advantageous as oxidative catalyst degradation is minimised. The self-assembled catalyst was more stable than when separated, because the reverse process, i.e. separation of the solution and complex from the support is unlikely because it is thermodynamically unfavourable. In order to maximise catalyst stability it was necessary to use an excess of phosphine (in this case P/Rh ≥3) , it has also been found that the 'dry' glass bead catalyst is more stable to storage.

The water content of the support has been shown to greatly affected the activity of the catalyst and the selectivity of the reaction.[63] Davis reported optimum activity for the rhodium catalysed hydroformylation reaction at a water content of ~8 %. At this level the catalyst had a high degree of mobility and yet is still available at the interface. At lower water content mobility was suppressed (the catalytic species are 'solid-like') as reflected by lower activity.[70] For example, the hydroformylation of 1-octene is characterised by a reduction in activity for a water content of more than 8 wt %. Also, the *n/iso* ratio and the system stability are reduced with increasing water content. It is thought that the resulting greater mobility of $[HRh(CO)(TPPTS)_3]$ promotes decomposition reactions. The activity difference of hydrated (~9 wt % water) and 'dry' glass bead catalyst (~2.9 wt %) has been reported to be typically two or more orders of magnitude.

The site of the reaction is well established. On supports with physically different structures, the activity depends upon the specific surface; that is the reaction takes place at the phase boundary. In its isolated state [$HRh(CO)(TPPTS)_3$] the solid contains up to 16 wt % water - a "primitive SAP catalyst". In the hydroformylation of 1-octene in cyclohexane, the results almost matched values with SAP catalysts: 98.7% conversion, *n/iso* 2.1-2.9.[72] As the Rh complex is insoluble in the organic reactants, the reaction must take place at the solid/liquid interphase. For classical liquid/liquid systems, the rate of hydroformylation decreases in the series 1-hexene>1-octene> 1-decene; with the SAP catalytic method, these alkenes react at virtually the same rate. Typically for surface effects, the solubility of the alkene in the aqueous phase is no longer the rate determining factor.

Thus, in summary Davis has demonstrated that the catalytic activity of these systems is similar to conventional homogeneous reactions for hydroformylation reactions. The precise operating mode of these catalysts and the nature of their interactions with the support are still a matter of debate. Thus, the stability of the catalysts towards metal leaching and the optimum amount of water necessary to achieve high activity are both dramatically dependent on the catalyst precursor system and the reaction itself. For example, in the hydroformylation of octene with $HRh(CO)(TPPTS)_3$ the amount of water required was sufficient to fill the pores of the support. However, above a certain amount of water, severe problems of metal leaching and/or stability of the catalyst were observed. Furthermore, he has shown that the individual catalyst components can self-assemble, implying that the reverse process, which leads to leaching, is unlikely. Indeed, the contamination of products from these systems with transition metal residues is negligible.

Horváth has also commented on the importance of water content on the support.[65a]

By starting from a high water content the activity of the catalyst in a trickle bed reaction was seen to increase as water leached from the bead into the organic layer until the water content was only sufficient to supply two monolayers to the surface of the controlled pore glass bead. This corresponds to the greater presence of active sites of the mobile catalyst at the interface, instead of a catalyst immersed in the supported solvent. It was proposed that the hydrophilic support held water soluble phosphines by the hydrogen bonding of the hydrated sodium-sulfonate groups to the surface.

Other groups have investigated improving the overall reaction of the SAPC. Yuan and co-workers co-deposited alkali metal salts on the surface of the beads prior to hydration to improve activity and *n/b* ratios.[73] Tóth *et al* synthesised HexDPPDS in order to attempt to make the ligand more surface active, reasoning that the lipophilic chain would bring the metal closer to the interface.[74] The ligand was in fact less active than TPPTS.

Frémy *et al* demonstrated the hydroformylation of α,β-unsaturated esters using the supported aqueous phase catalysts to give higher turnover frequencies than the analogous homogeneous and biphasic reactions.[66b] Methyl acrylate, a polar substrate, was subjected to the hydroformylation reaction using a silica support and the average turnover frequencies were over ten times greater than those observed for the analogous biphasic and homogeneous reactions. This was ascribed to the beneficial interactions between methyl acrylate, supported solvent and the surface hydroxyl groups. The great dependence on water content was noted here again. In contrast to Davis' results for non-polar substrates, they investigated polar substrates and found substrate functionality played a major factor. Optimal conditions were observed with total pore filling on the support as shown by an increase in activity and when the water content exceeded filling all pores the activity dropped rapidly to approach that of the biphasic system. Substrates which were less polar than methyl acrylate reacted with optimal activity at low pore filling, where a large surface area contact was essential.

Mortreux *et al* displayed elegantly that the specificity of biphasic systems compared well to those anticipated for single phase systems.[66a] They performed a regioselective hydroformylation of methyl acrylate to give α-formylpropionic acid with the catalyst $[HRh(CO)(TPPTS)_3]$, to provide an aldehyde yield comparable to that achieved with TPP, as well as an α/β product ratio of the expected order of magnitude and an even higher turnover frequency (TOF).

Use of alternative supported hydrophilic layers in the hydroformylation reaction has been investigated by Naughton and Drago, who termed their system as supported homogeneous film catalysts (SHFCS).[75] They employed high boiling point liquid or liquid polymers (polyethylene glycol - PEG) in combination with the catalyst $HRh(CO)(TPPTS)_3$ on the surface of silica in an analogous manner to the Davis preparation hoping that they would increase the viscosity of the film, retain the catalyst more efficiently and that the film would be insoluble in the substrate and product.

The very viscous PEG and alternative films of polyvinylpyrrolidine, polyethylene oxide and polyvinylalcohol showed drastically reduced activity or none at all.
Other transition metals have been employed as catalysts in SAP hydroformylation reactions such as cobalt[65b] and platinum[65c] but have generally shown less activity than their rhodium counterparts.

1.5.3 Hydrogenation reactions

With SAP catalysts based on Ru-TPPTS complexes, the selective reduction of α,β-unsaturated aldehydes to allyl alcohols can be performed.[67] The non-supported solid catalyst showed little activity in the reaction in contrast to the supported catalysts. Thus, at 100 bar pressure of H_2, 3-methyl-2-butenal **9** was reduced in almost quantitative yield and high selectivity (up to 89%) to give 3-methyl-2-butenol **10**. The reduction in activity on recycling the catalyst material was attributed to successive adsorption of the reactants onto the beads which causes catalyst poisoning. Metal loss only dominated when polar solvents such as methanol were used in the reaction.

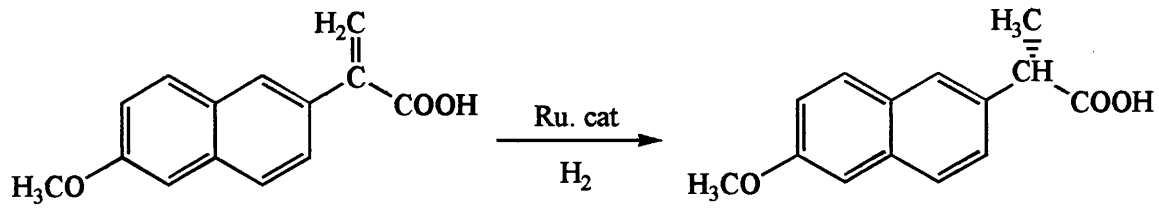
Asymmetric hydrogenation

Wan and Davis have reported the first example of asymmetric catalysis in neat water where the enantiomeric excess obtained was as high as that observed in non-aqueous solvents.[76] Using a Rh(I) catalyst with a tetrasulfonated BINAP ligand, an e.e of 70.4% was observed for the hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid in neat water; the unsulfonated catalyst gave an e.e of 67%. The synthesis of naproxen **27** from 2-(6'-methoxy-2'-naphthyl)acrylic acid **26** was the reaction under study in all of the experiments. While the BINAP ligand has proven useful for many asymmetric reactions, the variety of Rh(I) catalysed reactions proved rather limited. Ruthenium complexes show hydrogenation activity for a broader range of substrates and hence were deemed suitable for the task. Wan and Davis prepared a Ru analogue of their Rh-BINAP complex.[77] Ligand modification was accomplished with tetrasulfonated BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl], which in conjunction with ruthenium dichloride generated the active hydrogenation complex [Ru(BINAP-4-SO_3Na)(C_6H_6)-Cl]Cl. It revealed superior enantioselectivity and stability to the corresponding Rh complex.

For certain substrates, the e.e's were lower in neat water than in organic media. However, others have demonstrated either equal or higher e.e.'s with water than in non-aqueous solvents. Another asset in the use of ruthenium is that it can be used in water well above room temperature; the rhodium catalyst is not stable above room temperature.

The water-soluble, asymmetric, hydrogenation catalyst represents a significant step towards a viable asymmetric process in environmentally benign solvents. However, with all homogeneous processes it still suffers from catalyst separation problems. Wan and Davis have developed an SAPC using the water-soluble Ru-BINAP complex.[68a,b] The SAPC is only seven times less active than the homogeneous analogue, but 50 times more active than an ethyl acetate/water two-phase reaction mixture in the hydrogenation of the naproxen precursor. This is due to the much larger interfacial area resulting from the controlled-pore-glass support. Testing of the filtrate suggested that no soluble ruthenium species leached into the organic phase.

Further developments of this reaction came in the form of substitution of the water phase with water-soluble ethylene glycol in the identical enantioselective hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid **26**.[68c] The reaction led to the important non-steroidal anti-inflammatory drug (*S*)-naproxen **27** with e.e values as high as 96%. Davis realised the practical preparation of a recyclable heterogeneous catalyst for asymmetric hydrogenation displaying high activity and enantioselectivity directly comparable to that of its homogeneous counterpart (88.4% vs. 88.2% at r.t., increasing to 95.7% @ 3 °C).

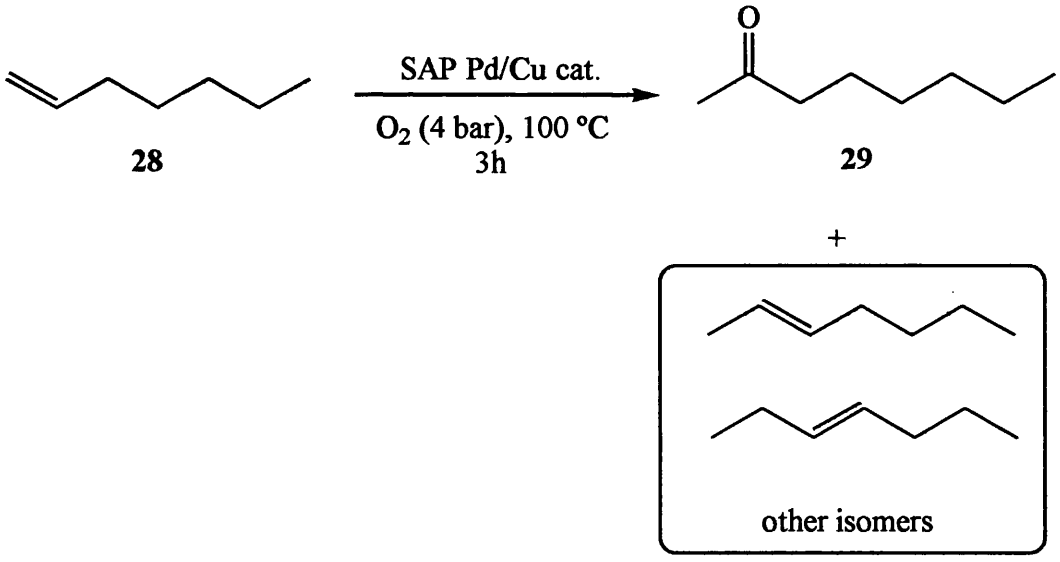


26 **27**

Additionally, Tóth *et al* synthesised and utilised rhodium complexes of water soluble derivatives of enantiomerically pure bidentate phosphine ligands for asymmetric hydrogenation.[78]

1.5.4 Wacker oxidations

The Wacker process is a palladium/copper partial oxidation of an alkene.[79] One feature of this reaction is that although the oxidant is molecular oxygen, the incorporated oxygen comes from water,[80] hence the reaction is usually carried out in aqueous solvent which retards the oxidation of sparingly soluble higher alkenes, a limitation which may be overcome by SAPC. To compare performance with SAP catalysts, $PdCl_2$ and $CuCl_2$ (1/1) were immobilised on CPG-240 (15 wt % H_2O).[81] In 3 h, this catalyst converted 1-heptene **28** at 100 °C, $p(O_2)$ = 4 bar, and an alkene/Pd ratio of 210/1 into 2-heptanone **29** (oxidation), 2-heptene, and 3-heptene (*isomerisation*) as illustrated below. Conversions of 1-heptene under optimal conditions were found to be of the order of 25% with significant isomerisation. In the conventional Wacker process, isomerisation is negligible.



In the SAP catalytic process, the oxidation of Pd^0 to Pd^{2+} is probably very slow, so isomerisation at the stage of the Pd-alkene complex became more significant. Isomerisation was reduced by increasing O_2 partial pressure with a more rapid Cu^+ oxidation. At temperatures above 100 °C the conversion and selectivity rapidly fall off, reflecting the domination of isomerisation at higher temperatures. No leaching of copper or palladium was observed down to the detection limits of 1 and 2 ppm respectively.

In spite of the unfavourable product distribution, SAP catalytic technology has the advantage that use of corrosive solutions of Cu^{+} is avoided. The latter problem affects all conventional Wacker processes. Hence, this methodology may have potential for use in extracting other metal contaminants after the metal catalysed reaction has gone to completion.[82]

Conclusion

The implementation of new catalytic technologies with a view towards more environmental regulation for the problematic separation of catalyst from product have been addressed. The disposal of the catalyst system (catalyst, solvent) must be of utmost importance when approaching catalytic reactions, especially for multi-scale purpose. There is without doubt a movement from liquid catalysts to solids and from organic-based to aqueous-based solvents. Nowadays, environmental legislation demands strict specifications for the levels of metal in the final product and thus the complexity of the catalyst is likely to increase. Thus it seems more prosperous to develop a new type of catalyst rather than introduce further clean-up processes.

Supported aqueous phase catalysis (SAPC) seems to provide the ideal solution to all the quandaries arising from the homogeneous system. It unites the assets of both solid supports and water-soluble ligands to produce a unique type of catalysis. A fair amount of effort has been injected into developing this area of catalysis for improving hydrogenation, hydroformylation and other universally utilised catalytic reactions. Hence, it seemed logical to apply the theory behind the technique to various palladium-catalysed reactions which is directly related to the work performed in the group. Ultimately we would aim to show the benefits of the new catalyst system and demonstrate the scope for such work in the future. It would be in our interest to be able to synthesise a catalyst for day-to-day usage in a diverse range of palladium-catalysed reactions for industrial operations.

CHAPTER 2

HECK REACTIONS USING GLASS BEADS

2.1 Introduction

In the 1970's a Japanese and American group simultaneously designed and executed palladium-catalysed coupling reactions of aryl- and alkenyl halides with alkenes.[83] In subsequent investigations Richard Heck and his group demonstrated the utility and rather broad scope of this new catalytic transformation. Only within the last decade has this powerful C-C bond forming process been exploited to its full synthetic potential and the Heck reaction[84] is now recognized as an indispensable method in organic synthesis.[85] This reaction has a diverse range of applications from the preparation of novel polymers, hydrocarbons and dyes to the new advanced enantioselective syntheses of natural products.

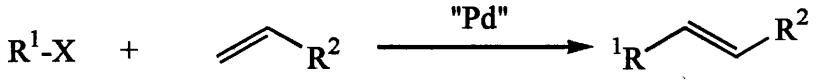
The Heck reaction is one of the true "power tools" in contemporary organic synthesis.[86]

2.2 Mechanism

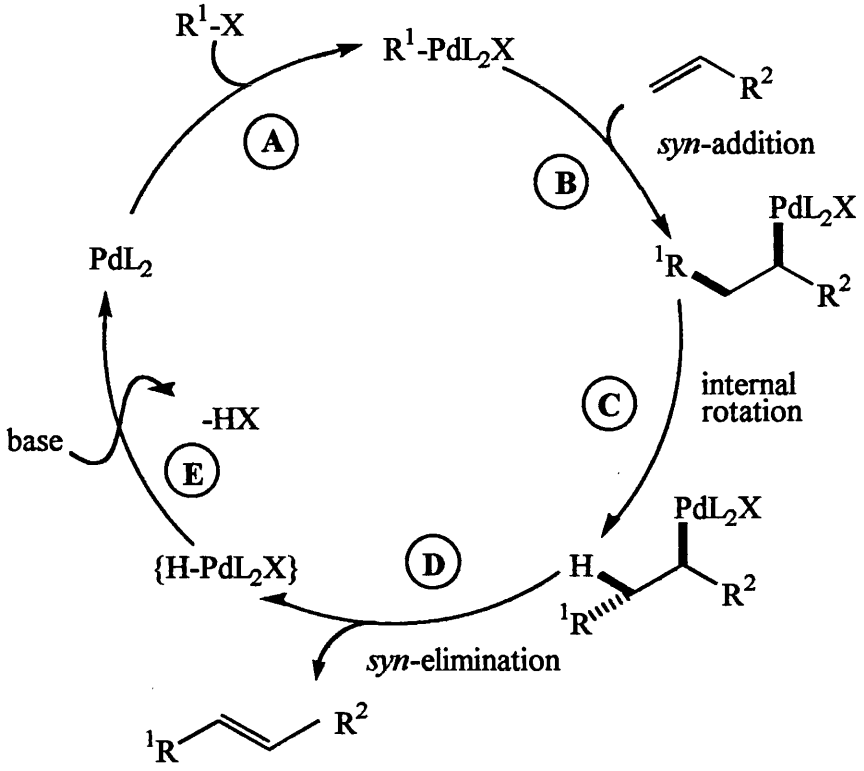
From the origin of the evolution of the Heck reaction into a facile method for the preparation of alkenyl- and aryl- substituted alkenes, reasonable concepts for the mechanism have emerged, which serve as a working hypothesis (**Scheme 8**).

Commercially available palladium compounds in the presence of various ligands are frequently used as catalysts. The first choice is often the air stable and relatively inexpensive palladium acetate, however, several other palladium sources are preferable in certain applications. It is commonly assumed that the palladium (II) species is reduced *in situ* by the solvent, the alkene,[87] the amine[88] or the added ligand (frequently a phosphane, which is oxidised to a phosphane oxide).[89] Thus, the coordinatively unsaturated 14-electron palladium (0) species produced, is usually coordinated with weak donor ligands (usually tertiary phosphines) and is assumed to be the catalytically active complex.

In the first step of the catalytic cycle (**A** in **Scheme 8**) a haloalkene or haloarene is commonly assumed to add oxidatively to the coordinatively unsaturated palladium (0) complex, generating a σ-alkenyl or σ-arylpalladium (II) complex.[90] As the electrophilicity of this complex is enhanced, it more readily accepts an alkene molecule in its coordination sphere, probably by exchange for another ligand.



R^1 = alkenyl, aryl, allyl, alkynyl, benzyl, alkoxycarbonylmethyl
R^2 = alkyl, alkenyl, aryl, CO_2R', OR', SiR_3' etc.



Scheme 8

If the alkenyl (aryl) residue and alkene ligand on palladium are in a *cis*-orientation, rotation of the alkene can lead to its in-plane coordination, and subsequent *syn*-insertion of the σ-alkenyl- or σ-arylpalladium bond into the C-C double bond occurs to yield a σ-(β-alkenyl)- or σ-(β-aryl)alkylpalladium complex via a four-centered transition state (**B**).

After *cis*-addition of the alkene, the reaction-terminating β-hydride elimination (**D**) can occur only after internal rotation (**C**) around the former double bond, as it requires at least one β-hydrogen to be orientated synperiplanar with respect to the halopalladium residue.[91] The ensuing *syn*-elimination yielding an alkene and a hydridopalladium halide is, however, reversible, and therefore the thermodynamically more stable (*E*)-alkene is generally obtained when the coupling reaction is performed with a terminal alkene.

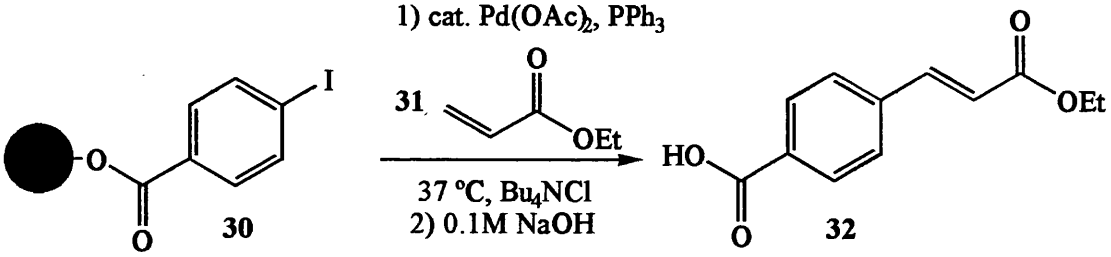
Reductive elimination of HX from the hydridopalladium halide, aided by the added base, regenerates the catalyst (**E**) and thereby completes the catalytic cycle. The mechanism has not been proved in all details, and the rate-determining step remains ambiguous. Often, oxidative addition has been assumed to be rate-determining, however, some doubt has been cast on this hypothesis too.[92]

2.3 Solid supports in Heck reactions

Immobilisation of the active catalyst onto a polymeric support offers many advantages such as a high turnover number, easy separation from products, recyclability, high thermal stability and moderate catalytic efficiency. Some solid supports attach to the substrate rather than the catalyst itself and both methods of preparation will be reported.

2.3.1 Solid supports attached to substrates

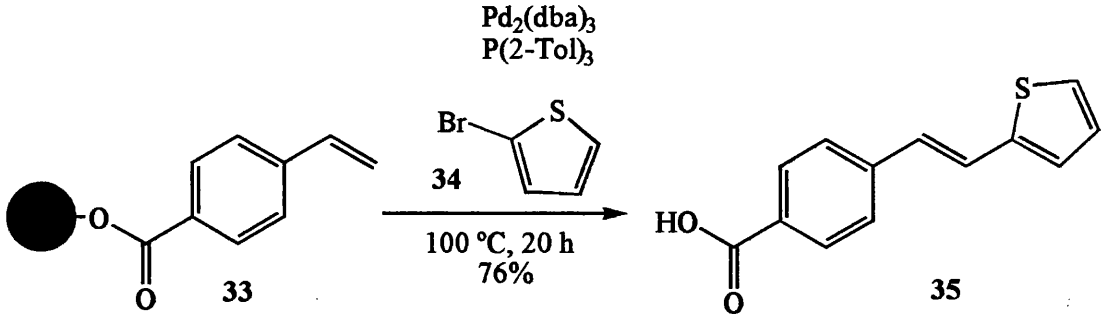
Zhou *et al* attached hydroxyl functionalised TentaGel resin to 4-iodobenzoic acid **30** and coupled it to ethyl acrylate **31** with use of Bu_4NCl as phase-transfer agent to give the coupled product **32**, after removal of the resin.[93]



Solvent DMF/H_2O	Time (h)	Conv. (%)
0 / 100	18	47
90 / 10	4	>95

The choice of solvent had a significant effect on yield and reaction time. The resin was washed with DMF and methanol with subsequent detachment from the solid support with sodium hydroxide.

Yu *et al* immobilised model compounds 4-vinyl- and 4-iodobenzoic acid on Wang resin and reacted them with a series of substrates under Heck conditions.[94] One such reaction involves coupling 2-bromothiophene **34** with 4-vinylbenzoic acid **33** using harsher conditions to perform coupling effectively as illustrated below. The coupled heterocycle **35** is produced in good yield.

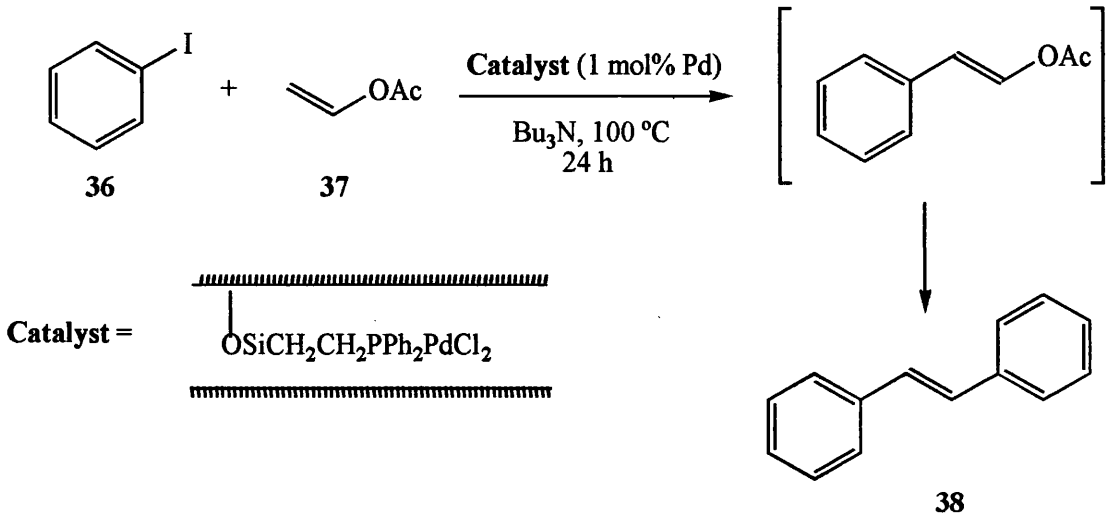


With a few exceptions, such as ethyl propionate which did not react under the chosen conditions, alkenes and alkynes were obtained in high yield.

2.3.2 Solid supports attached to palladium catalysts

Use of polymer-bound palladium catalysts for cross-coupling reactions have been studied, but the identity of the catalytically active species remains controversial. Hallberg *et al* have suggested that the active state in the arylation of methyl acrylate with iodobenzene on polystyrene-supported palladium catalysts is metallic palladium.[95] Arylacetaldehydes have been synthesised in moderate yield via a Heck reaction using the polymeric catalyst Polymer-phenyl-(1,10-phenanthroline)-palladium(0).[96] Thus, Zhuangyu *et al* treated iodobenzene with acrylamide under traditional Heck conditions by using tributylamine as base and palladium acetate as catalyst to yield (*E*)-cinnamamide in good yield (80%). Unfortunately, an extensive loss of catalytic activity was observed after several cycles due to palladium leaching from the polymer support. They thought this was caused by competitive complexation of tributylamine existing in the reaction media towards the metal. Thus they employed sodium acetate and DMF in place of tributylamine and found the catalyst remained intact and could be re-used in the reaction to give high yields.

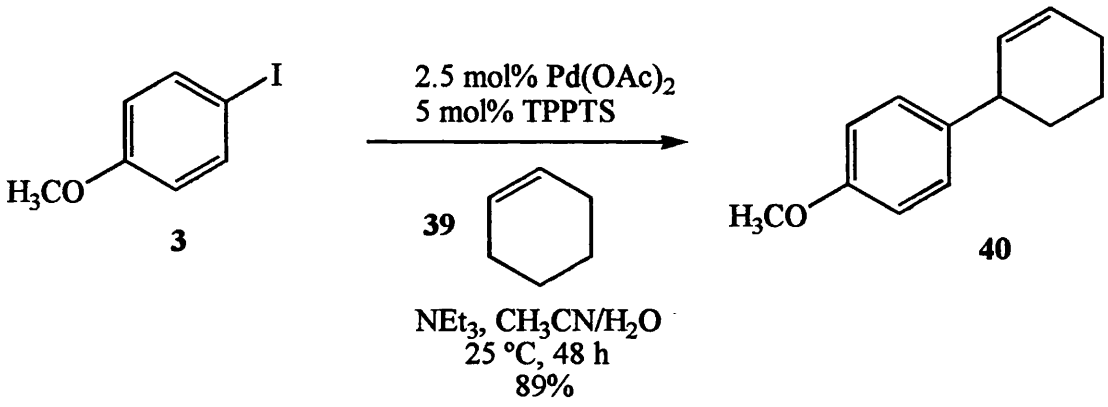
Li *et al* reported use of palladium on porous glass tubing as a heterogeneous catalyst for liquid phase organic coupling reactions carried out in air and in the absence of ligands.[97] Another group performed a single pot reaction for substitution and cross-coupling of vinyl acetate **37** with iodobenzene **36** forming *trans*-stilbene **38** in good yield by interlamellar montmorilloniteethylsilyldiphenylphosphinepalladium(II)chloride catalyst as depicted below:-[98]



The most-used polymer backbone is polystyrene, crosslinked with 1 or 2% vinylbenzene. These resins withstand a wide range of reaction conditions, but certain limitations are observed. Prolonged use of mechanical stirring can cause mechanical damage of the resin and the working temperature range is -78 °C to 155 °C. Solid-support reagents cannot be used because of the problems of solid-solid interactions and polymers require excessive washing procedures in order to remove excess reagent and high boiling solvents from large interior spaces in the resin.

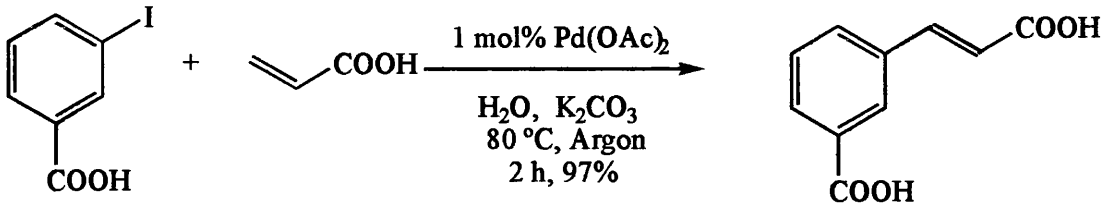
2.4 Water-soluble ligands in Heck reactions

Many reactions are now performed in aqueous media as it is environmentally friendly. The presence of water has been found to accelerate certain Heck reactions,[99] and consequently the development has involved use of water-soluble triarylphosphane ligands (e.g. triphenylphosphane *m*-sulfonate sodium salt (TPPTS)[100]) with which many alkene arylations can succeed effectively in aqueous solvent mixtures.[101] One such example is exemplified by the palladium-mediated coupling of aryl iodide **3** with cyclohexene **39** which proceeded at room temperature to yield a single aryl adduct **40** in good yield as described below:-



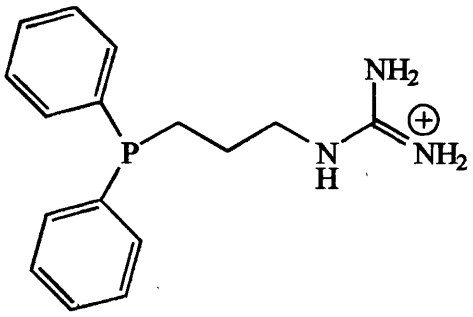
The arylation of ethylene under aqueous or aqueous-organic solvent two-phase conditions has been studied using $PdCl_2L_2$, where L = $(C_6H_5)_2P(m\text{-}C_6H_4SO_3Na)$ i.e. TPPMS to give styrenes in good yields.[102] Stelzer *et al* also exploited water soluble phosphines and employed them in palladium-catalysed cross-coupling reactions between diphenylphosphine or phenylphosphine and substituted aryliodides.[103]

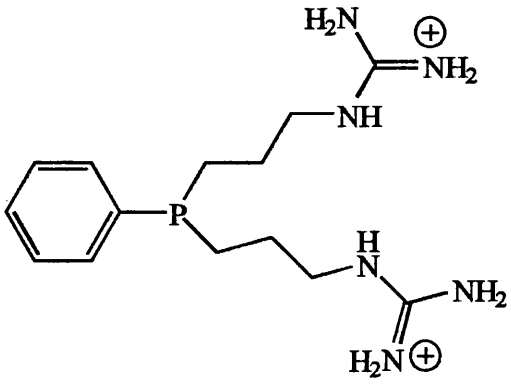
Palladium-catalysed reactions of aryl halides with acrylic acid and acrylonitrile gave the corresponding coupling products in high yields with a base ($NaHCO_3$ or K_2CO_3) in water as solvent. For instance, the reaction of *m*-iodobenzoic acid **1** with acrylic acid **41** in the presence of potassium acetate as base gave the substituted product **42** in excellent yield after two hours, as depicted below:-[104]



1 **41** **42**

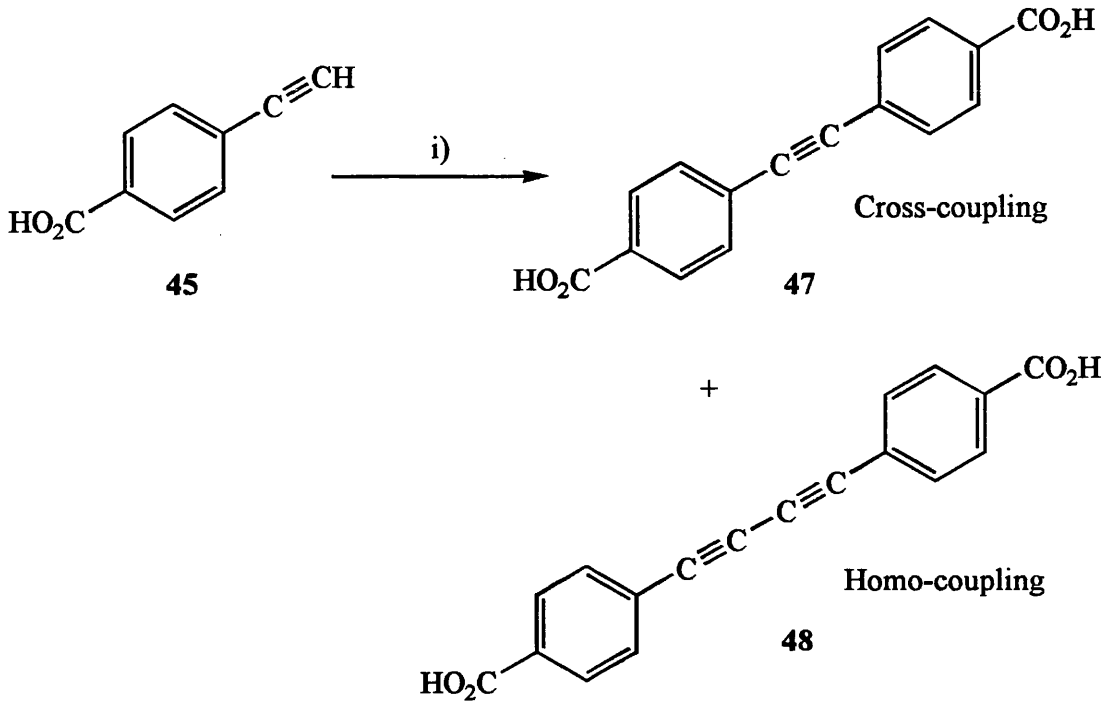
Water-soluble cationic phosphine ligands containing *m*-guanidinium phenyl moieties have been synthesised for applications in aqueous Heck reactions.[105] The two guanidino phosphines synthesised **43** and **44** are represented below:-





43 **44**

The cationic phosphines were readily soluble in water and are considerably less susceptible to oxidation than TPPTS. The ligands were tested and compared with TPPTS as ligand in the coupling of 4-iodobenzoic acid **46** with *p*-carboxyphenylacetylene **45** using typical Heck conditions as illustrated below:-



i) 5 mol% $Pd(OAc)_2$, 10 mol% CuI, *p*-$(HO_2C)C_6H_4I$ **46**
50% CH_3CN/H_2O, 50 °C

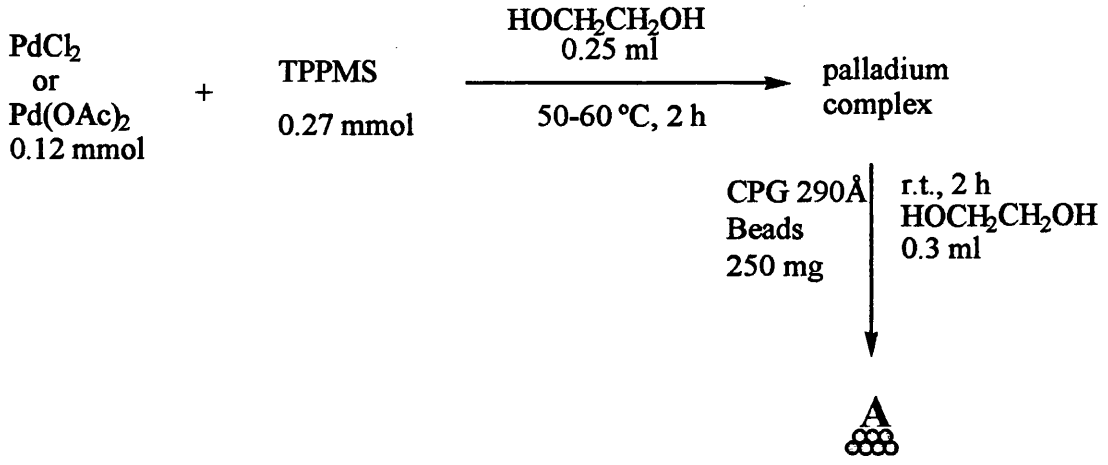
In 50% aqueous acetonitrile, the reaction rate was faster than in water alone, but the effect on chemoselectivity was not uniform. With TPPTS, exclusive formation of the cross-coupled product **47** (100%) was found using either carbonate or triethylamine as base. On the contrary, the selectivity ratio was much less pronounced with the guanidino ligands (both cross- **47** and homo-coupling **48** products were observed).

2.5 Optimisation of the Heck reaction with beads

The aim of this project was to maintain the activity and selectivity of the homogeneous system whilst concentrating on minimising leaching of the catalyst into the product (clean technology). This is of paramount importance from a pharmaceutical perspective to ensure that no palladium (or lower than specification requirements) is present in the pure drug. We also wished to combine the merits of both solid supports and water-soluble ligands in a model catalyst. Thus we decided to employ a supported aqueous-phase catalyst[5] to allow immobilisation of our palladium catalyst on the solid support.

Exploratory work focused on developing a suitable catalyst system whereby the catalyst complex was held in solution in a polar, hydrophilic film supported upon porous glass beads, (controlled pore glass, CPG) whilst the products and reactants were restricted to a non-miscible solvent phase. Several factors were considered in the preparation of the supported catalyst with the aim of ensuring good assembly, distribution and immobilisation of the catalyst complex across the surface of the beads.

The supported catalyst was prepared as detailed in **Scheme 9**. The palladium catalyst (either palladium chloride or palladium acetate) was treated with 2.2 equivalents[106] of the polar ligand TPPMS in a minimal amount of ethylene glycol. After heating to ensure complexation, controlled-pore beads were added as well as additional ethylene glycol. After stirring, to facilitate an even coating of the beads, they were cooled and rinsed with reaction solvent three times to remove any residual unreacted material. The beads **A** were then ready for use as a catalyst in the Heck reactions.

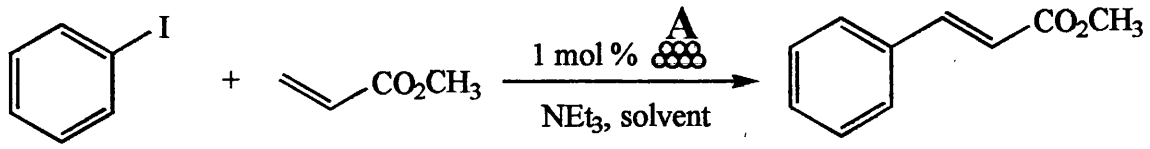


Scheme 9

Beads **A** will be represented as shown above throughout the discussion section.

It is believed that the immobilisation is due to strong interactions between the sulfonated groups of the phosphine and the polar ethylene glycol surrounding the glass beads. Hence a substantial amount of work has been performed on optimising the bead complex.

The coupling of iodobenzene **36** with methyl acrylate **49** was investigated using standard Heck conditions to give the cinnamate product **50**.



36 **49** **50**

It was assumed that the palladium catalyst was reduced by the TPPTS to form Pd (0) before the Heck reaction could occur. After the reaction had gone to completion, the reaction mixture was decanted off, examined for purity, yield of product and absence of palladium impurities and compared with single phase reactions.

Various conditions were tried to optimise bead preparation in the Heck reaction.[107]

i) Solvent

Many solvent systems were investigated of varying polarity [from the non-polar (hexane:ether mixes) through to the more polar acetonitrile]. It was concluded that polar solvents (e.g. acetonitrile) caused disintegration of the organometallic complex from the beads and rapidly deactivated the catalyst. The high percentage of metal recovered in solution suggested that the dissolution of the metal was the reason for the deactivation in polar media. Thus, the concept of utilising beads **A** seemed to be limited to fairly non-polar media, probably because of the strength of the interaction of the hydrophilic phosphine with the polar alcohol groups in the ethylene glycol decreased in a polar solvent. Although this parameter was not measured, it is possible that the ethylene glycol film on the catalyst surface was destroyed in a protic polar solvent, such as methanol. Hence, it is requisite to have a fairly non-polar solvent system for the reaction to be successful.

ii) Temperature

The reaction was performed at room temperature (see **Table 2**) but the reaction time and yield were inferior to the reactions heated to reflux. A control reaction was tried using all components of beads **A** but no beads were added thus the palladium complex was introduced into the reaction. This gave high levels of palladium leaching so it showed that beads were essential to prevent leaching of palladium into the organic phase.

iii) Bead preparation

The amount of beads added to the palladium complex was varied for process optimisation in terms of minimising palladium leaching, maximising yield and obtaining a reasonable reaction time for the reaction. The results showed that in general the reaction time appeared to increase with the addition of more beads and evened out to reach a plateau. Eventually the addition of more beads resulted in no increase in reaction time.

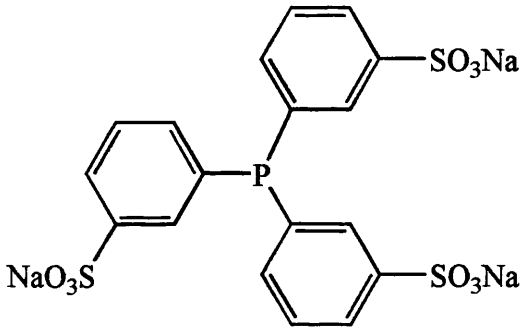
In terms of palladium leaching, with a low quantity of beads high leaching of palladium was observed. This is thought to be due to an excess of the palladium complex compared to beads. With a large quantity of beads, a high amount of palladium leaching was observed also. It is suspected that there was an insufficient amount of ethylene glycol to coat the beads and this prevented impregnation of all the complex onto the beads. This hypothesis was confirmed by using a large amount of beads with twice the normal quantity of ethylene glycol (which should fill the pores and coat the beads adequately to make the catalyst mobile). Results showed no leaching was observed after the reaction. The results can be compared to the results obtained by Davis *et al* (see section **1.5.2**).

iv) Hydrophilic nature of ligand

In an attempt to reduce palladium leaching further, investigations into the use of trisulfonated triphenylphosphine (**8**) occurred. We hoped this ligand would bind more tightly to the beads due to the presence of more hydrophilic sulfonate groups which would bind to the ethylene glycol.

The trisulfonated triphenylphosphine ligand was synthesised by direct sulfonation of triphenylphosphine using 20% fuming sulfuric acid, which proved straightforward, although the work-up procedure was cumbersome and led to reaction mixtures that contained 75-85% TPPTS and 15-25% TPPTS oxide.[108]

More recently, Herrmann *et al* reported a new process for sulfonation of phosphane ligands whereby they found that addition of orthoboric acid lessened phosphane oxidation or suppressed it completely with some ligands.[109] Unfortunately, for TPPTS no significant change in oxidation was observed.



8 TPPTS

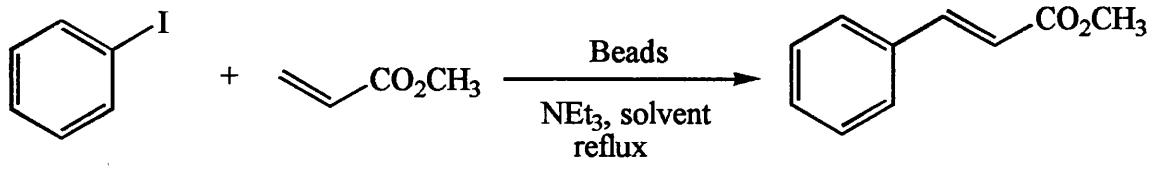
Beads **A** were produced as a green slurry which caused problems when trying to make the prepared bead complex in bulk as it was difficult to separate it into portions. Since beads **A** proved cumbersome in terms of having to pre-prepare the beads before each reaction it was decided to investigate improvements in the preparation procedure. One notion was to use a freeze-drying technique on the beads. The aim was to be able to synthesise the beads in bulk as a powder and re-activate them with ethylene glycol when required. Exactly the same preparation as in **Scheme 9** was utilised but the final slurry of beads were frozen and then freeze-dried to remove all ethylene glycol and produce a fine powder. These beads will be represented as **B** hence forth. The notion came from work carried out by Davis *et al*.[68b] The freeze-dried catalyst is stable and was re-solvated by dosing with ethylene glycol prior to use in reactions. Addition of 10% w/w ethylene glycol to the glass beads provided a robust and active catalyst.

v) Hydrophilic coating film

The effect of solvation (on the supported aqueous phase catalyst) upon activity proved to be very interesting. Maximum activity was attained at a loading of around 10 wt% (=0.1δ, theoretical film thickness =16Å) ethylene glycol to glass beads. At low loading (6.5Å theoretical film thickness of ethylene glycol), no activity was observed indicating a lack of mobility of the bead complex within such a thin film. Activity also decreased at higher loadings of ethylene glycol, presumably due to a diminishing interfacial area as all the pores became filled. Hence our results compared favourably with those observed by Hovárth *et al.*[65a]

Other coating materials in place of ethylene glycol were investigated such as poly(ethylene)glycol solid and liquid and poly(vinyl)alcohol. The preparation of the beads using these coating materials proved difficult as intractable solids were generated and the liquid poly(ethylene) glycol was viscous and could not be separated. The Heck reaction performed with these coating materials proved disappointing so ethylene glycol was the coating material of choice for further experimentation (see section **1.5.2**).

The prepared beads (various different preparations tested) derived from either palladium chloride or palladium acetate were examined for their ability to catalyse the Heck reaction. Thus, iodobenzene **36** and methyl acrylate **49** were treated with the prepared beads of choice (containing a 1 mol% palladium catalyst) in the presence of triethylamine and a suitable solvent (**Scheme 10**) to produce methyl cinnamate **50**. At the end of the reaction, the solution was decanted from the glass beads and analysed for the leaching of palladium.



36 **49** **50**

Scheme 10

Results from these experiments are detailed in **Table 2** below.

Table 2. The formation of methyl cinnamate **50** using the Heck reaction

Beads (type)	Pd catalyst	Ligand	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
A (CPG 290Å)	$PdCl_2$ [a]	TPPMS	Hexane:Et_2O 4 : 1	28	67	< 0.01 mg[b] < 0.1%
B (CPG 239Å)	$PdCl_2$ [a]	TPPMS	Hexane:Et_2O 4 : 1	25	71	< 0.01 mg < 0.1%
B (CPG 239Å)	$Pd(OAc)_2$ [a]	TPPMS	Hexane:Et_2O 4 : 1	25	63	< 0.01 mg < 0.1%
B (CPG 239Å)	$PdCl_2$ [a]	TPPTS	Hexane:Et_2O 4 : 1	25	75	< 0.01 mg < 0.1%
B (CPG 290Å)	$PdCl_2$ [a]	TPPMS	Hexane:Et_2O 4 : 1	48[c]	61	< 0.01 mg < 0.1%
C (Davisil 500Å)	$PdCl_2$	TPPTS	Hexane:Et_2O 4 : 1 (or $PhCH_3$)	3	69	< 0.01 mg < 0.1%
D (Davisil 500Å)	$PdCl_2$	TPPTS	$PhCH_3$	3	71	< 0.01 mg 0.3%
D (CPG 239Å)	$PdCl_2$	TPPTS	$PhCH_3$	3	70	< 0.01 mg < 0.1%
-	$PdCl_2$	TPP	$PhCH_3$	3	70	0.95 mg 18.3%

[a] Reactions used 0.13 mmol (1 mol%) Pd catalyst. [b] Calculations for Pd leaching are shown in the Appendix. Total amount of palladium chloride catalyst used in a reaction was 22.1 mg, thus, <0.01 mg of total palladium was leached into the final product i.e. <0.1%. [c] Reaction performed at r.t.

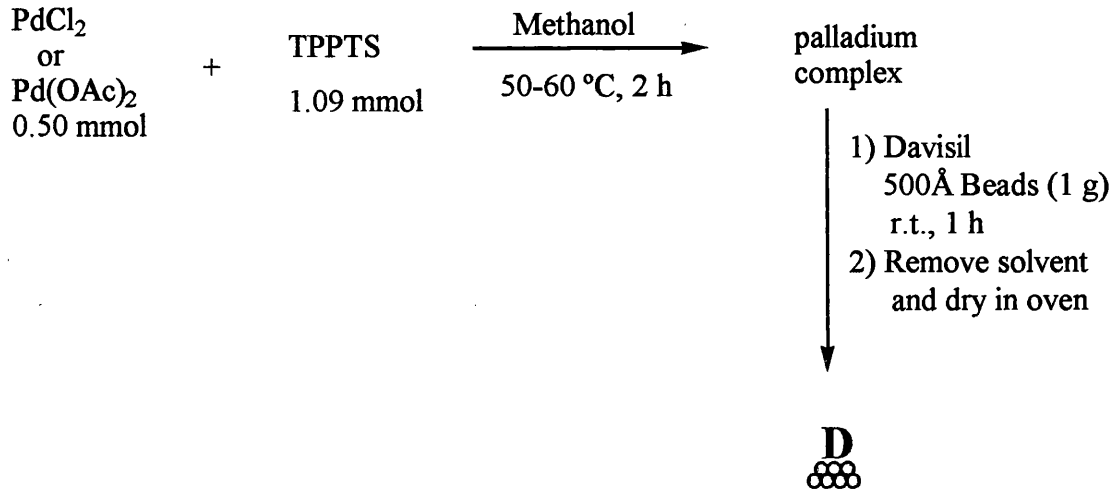
In **Table 2**, beads **B** composed of either of the two ligands (TPPMS **7** or TPPTS **8**) were compared and it was apparent that TPPTS gave better reactivity in terms of yield and, although palladium leaching was low in both cases, TPPTS actually gave minimal levels of palladium. These observations can be explained in terms of the interaction between the hydrophilic moiety of the catalyst complex and the molecules of the hydrophilic phase. The more hydrophilic phosphine (i.e. TPPTS) was held strongly in this interaction and this made leaching less likely.

Hence, the more polar ligand (TPPTS) was employed in all subsequent reactions. Catalyst loading and ratio of catalyst to ligand was studied by a colleague (Amin Mirza). Beads **B** were ideal for bulk production but it was found that reaction times were protracted, probably due to beads having to re-form during reaction to function as an effective catalyst.

An alternative preparation was derived from a self-assembly style[72a] (identified as Beads **C**) which basically entailed taking all the components that made up the supported catalyst (i.e. palladium catalyst, TPPTS, ethylene glycol, beads) and adding them directly to the reaction so the beads can "self-assemble". The results (see **Table 2**) for beads **B** and **C** using identical reaction conditions were compared and it was concluded that beads **C** were superior in terms of reaction time to beads **B**, but yields were reduced. Beads **C**, represented as 

provided a unique alternative. This method has been reported to produce a stable immobilised catalyst system, reduce deactivation of the catalyst and/or leaching from the support.

Davis *et al* reported that an aqueous film was an essential component of the bead complex for successful catalytic activity, whether it was water or ethylene glycol.[68a] The ethylene glycol (polar film) is thought to bind to the hydrophilic sulfonate groups in the ligand structure and adhere to the controlled pore glass beads. It was decided to test whether this was actually viable so beads **D** were synthesised as shown in **Scheme 11**.



Scheme 11

The palladium catalyst of choice was mixed with 2.2 equivalents of the polar ligand (TPPTS) and heated in methanol to dissolve (see the Appendix for a suspected structure of the palladium chloride-TPPTS complex). After 2 h the solution had changed from a brown to a green coloration ($PdCl_2$) or brown to grey ($Pd(OAc)_2$). After complexation Davisil beads were introduced and the reaction stirred at room temperature to ensure an even coating of beads onto the organometallic complex. The solvent was then removed *in vacuo* to yield a fine powder which was dried in an oven overnight to remove any residual solvent. The beads were used directly in reactions as a powder. The beads must contain only a minimal amount of solvent, and yet is still active for the Heck reactions, albeit with slightly higher levels of palladium leaching. As demonstrated in **Table 2** the beads provided reasonable yields, low palladium leaching and quick reaction times. Thus, we have shown in this case that an aqueous layer (ethylene glycol) was not required for activity. However, from investigations so far it appeared that ethylene glycol caused the reaction time to lengthen but lowered palladium leaching.

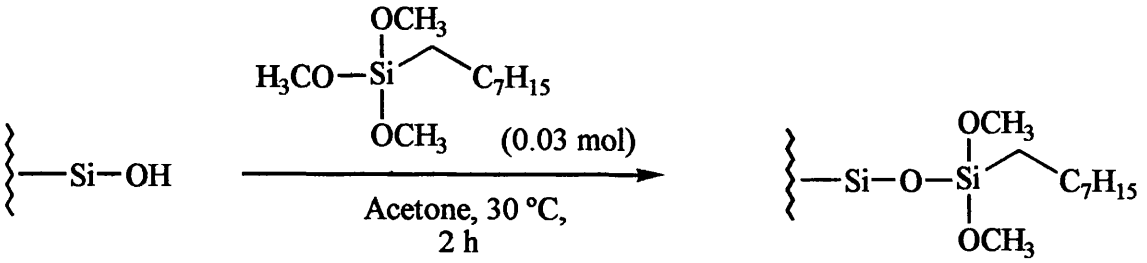
At this stage, it was thought suitable to see whether TPPTS was required for catalysis using a bead system. Hence, similar to the preparation of beads **D**, palladium catalyst (chloride in this case) was heated with *beads* (no TPPTS added) in methanol at 50-60 °C for 2 h to ensure the catalyst had adhered to the beads. The solvent was removed *in vacuo* to yield a fine brown powder.

The beads (containing 1 mol% palladium chloride) were tested in the ubiquitously utilised Heck reaction (**Scheme 10**) and the coupling reaction was unsuccessful after 48 h. Thus, the test proved the water-soluble ligand (TPPTS) was an essential component of the catalyst complex for catalytic activity.

Note also a change in the bead type used. A series of experiments were performed with different solvents and it was found that the Davisil beads compared well with the expensive CPG beads so it was decided to conduct further work using the cheaper Davisil beads.

Reverse phase supported catalysis

The ultimate aim of the work was to investigate a novel approach to supported homogeneous catalysis; the aim was to synthesise a complete reversal of the initial concept where a hydrophilic catalyst complex was held in solution upon a high surface area silica, whilst the products were restricted to a hydrophobic organic solvent. In this system a lipophilic catalyst complex was held on a high surface area porous silica bead by its affinity to the alkyl silane derivatisation of the surface of the glass. The substrates in the reaction were restricted to a bulk polar solvent allowing efficient catalysis without leaching of palladium into the reaction solvent. The beads (which have a high surface area and good pore size) were derivatised initially with silyl groups using a method adapted from Schott Engineering (**Scheme 12**).



Davisil 300Å
(10 g)

Derivatised Silica

Scheme 12

Octyl trimethoxysilane was chosen as it was able to impart lipophilic characteristics to the silica beads. Previous work (by Amin Mirza)[110] indicated that this alkyl silane showed promising results in other Heck reactions using polar substrates. The derivatised silane was produced by heating the silane with the Davisil beads in acetone and removing the solvent to produce a powder.

The derivatised silane was mixed with palladium acetate, hydrophobic ligand (triphenylphosphine **or** tri-(*o*)-tolylphosphine ligand) in cyclohexane with heating to ensure complexation and to produce fine powders. The beads are represented as

for the beads made with tri-(*o*)-tolylphosphine and 

for the preparation using triphenylphosphine as ligand.

vi) Recycle tests

It was necessary to determine how robust the supported catalyst was to degradation. Hence experiments were performed to test viability for recycling and re-use of the catalyst for an industrial process. Indeed, the beads were recycled several times and after each reaction the beads were rinsed several times with reaction solvent and subjected to a nitrogen atmosphere for an hour to remove excess solvent. Thus palladium levels were monitored and it was assumed that TPPTS/TPPMS remained attached to the bead as it preferred an aqueous environment.

The monosulfonated ligand was compared with the trisulfonated ligand in successive Heck reactions (**Scheme 10**) to show which gave the best activity. Palladium leaching was low in all cases but yields varied enormously.

The trisulfonated ligand afforded higher yields than the monosulfonated (17% after three consecutive reactions). Hence the monosulfonated ligand was excluded from further studies. It has been shown that excess TPPTS ligand stabilises the system against decomposition.[18] Thus, subsequent work employed the trisulfonated ligand.

As shown in **Table 3** with TPPTS as ligand, yields were reduced in subsequent reactions, which was thought to be due to the oxidation of phosphines rendered to a less competent catalyst. This was proved by disintegration of the bead complex by dissolving in methanol after the third reaction. The methanol solvent was removed *in vacuo* to yield a solid. To the solid was added deuterated water and the sample was analysed by ^{31}P NMR.

The analysis showed a greater level of phosphine oxide compared with the original ligand used in the initial experiment. Hence we can conclude that the non-active phosphine oxide is reducing the activity of the catalyst in the Heck reaction.

Kiviaho *et al* studied the same reaction using modified silica supports impregnated with various palladium catalysts.[111] They noted that after the first reaction, a small part of the palladium was released from the surface of the catalyst and this part had a high capability to catalyse the hydrogenation reaction and produce benzene and so decrease the selectivity for methyl cinnamate. In the second use, when the detached palladium was no longer *in situ* and the catalyst was totally heterogeneous, only the vinylation reaction proceeded and selectivity was virtually 100%. No significance in palladium leaching or any benzene by-product was found in the bead recycle tests.

A coordinatively saturated polymer-bound palladium (0) complex was measured for catalytic activity.[112] Kaneda *et al* noted that when re-using the polymeric complex, some loss of activity was found. They reasoned that this was not due to the lowering of the catalytic activity itself, but to the loss of polymer in the separation process.

Choplin *et al* also performed work on recycling supported aqueous phase catalysts in allylic substitution reactions.[113] They noted the activity of the catalyst was reduced after one recycle. They proposed that this might have originated either from a partial degradation of the catalytically active species or from a partial loss of water (hydrophilic coating film) during the first reaction test and/or during the washing procedure. No leaching of palladium was observed the product solution remained colourless. They managed to recover the activity by simple addition of water and re-ran the reaction to prove their findings.

Table 3. Recycle tests with TPP and TPPTS **8** as ligands

Beads (type)	Pd catalyst	Ligand	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
B  (CPG 239Å)	$PdCl_2$	TPPTS	1) 4	1) 75	1) <0.01mg <0.1%
			2) 5	2) 48	2) <0.01 mg <0.1%
			3) 8[a]	3) 36	3) <0.01 mg <0.1%
D  (Davisil 500Å)	$PdCl_2$	TPPTS	1) 3	1) 70	1) <0.01mg <0.1%
			2) 27	2) 51	2) <0.01 mg <0.5%
			3) 46	3) 37	3) <0.01 mg <0.6%
D  (Davisil 500Å)	$PdCl_2$	TPPTS and TPP	1) 21	1) 75	1) <0.01mg[b] <0.1%
			2) 34	2) 56	2) <0.01 mg <0.1%

[a] Each reaction was performed two or three consecutive times using the same conditions and reaction time, yield and Pd leaching was noted for each reaction. [b] Total amount of palladium chloride used in reaction was 4.4 mg, thus <0.01 mg of total palladium leached into product, i.e. <0.1%.

Hence, it was decided to pursue work with TPPTS as the ligand as it seemed more stable to the reaction conditions. Triphenylphosphine (TPP) (1 eq. w.r.t. TPPTS) in combination with TPPTS was investigated to try to reduce oxide levels by oxidising TPP in preference to TPPTS. This idea seemed to have some use in preventing TPPTS oxidation but the reaction time was increased.

Different batches of the same beads were also checked to show reproducibility of results in the same Heck reaction (**Scheme 10**). For all batches, reactivity, yield and Pd levels remained fairly constant so bead preparation seemed consistent. Hence, this showed there was an even coating of the palladium complex on the beads and that this was catalytically well defined.

Conclusions

It has been demonstrated that the model bead preparation for the Heck reaction worked effectively in terms of solvent, temperature, bead composition and coating material. Several types of beads have been prepared for application in the reaction and all have their own merits. TPPMS was found to be inferior to TPPTS as ligand and thus no further studies were investigated with this ligand. We also noted that both TPPTS and the bead were essential components of the catalyst system.

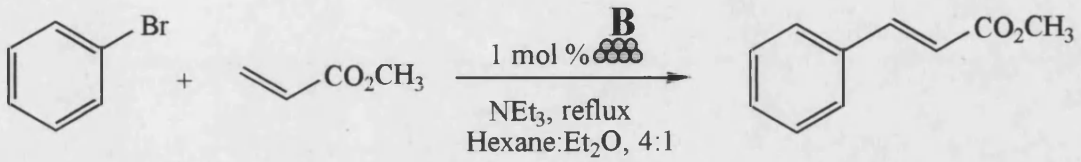
Supported aqueous phase catalysts offered many advantages over the homogeneous system such as stability of the catalyst, activity, recyclability, and of paramount importance, no or minimal palladium leaching. Any phosphine leaching was removed in aqueous work-up unlike TPP which remained present in the product.

For the cinnamate reaction, with all bead preparations extremely low palladium leaching into the organic media (<0.1%-0.3%) was observed, compared with the homogeneous reaction (18.3%). Thus the objective to reduce the palladium content of the product has been achieved. Other Heck reactions were examined to test the scope of this methodology.

The results with the recycled beads proved promising. Although it was not possible to maintain the activity in subsequent reactions, it could be envisaged that by loading the beads into a continuous flow type reactor, the Heck reaction could be maintained by adding starting material constantly and decanting off the product as it was produced. This way the catalytic cycle would be constantly in use and, hopefully, as soon as palladium reduced to palladium (0) it would be oxidised back to palladium (II) immediately. When performing three repetitive reactions it is likely that the catalytic cycle was interrupted, and at this stage, oxidation of the TPPTS to phosphine oxide (which is inactive) would occur.

2.6 Other Heck reactions using the various bead complexes (A-E)

The formation of methyl cinnamate **50** using bromobenzene **51** as halide source and methyl acrylate **49** proved encouraging with beads **B**. However, the yields and reaction times were less fruitful than with iodobenzene. This could be expected as the nature of the leaving group greatly affects the reaction and aryl iodides react more quickly than bromides.[114]

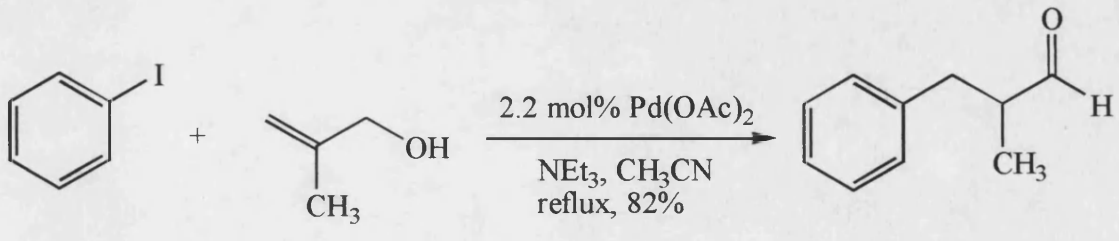


51 **49** **50**

Pd catalyst	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
$PdCl_2$	46	54	<0.01 mg <0.1%
$Pd(OAc)_2$	48	47	<0.01 mg <0.1%

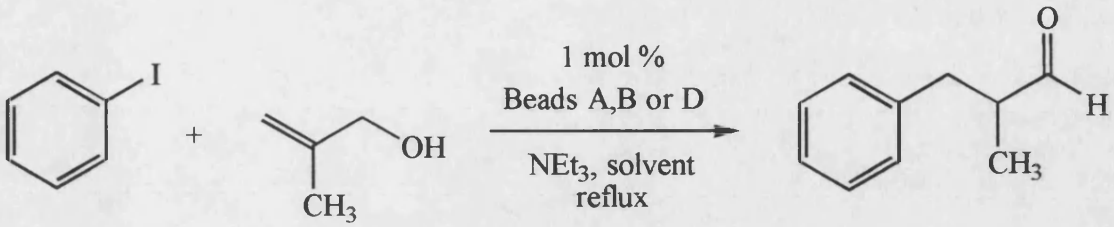
N.B. palladium leaching levels in the reactions were extremely low, i.e. <0.01 mg of the total palladium catalyst used in the reaction leached into the product which equates to <0.1% of maximal palladium (0) that could potentially leach.

A useful variation of the Heck reaction occured with allylic alcohols. In most instances, palladium hydride elimination produced vinylic alcohols which isomerised to β-arylcarbonyl derivatives.[115] Methallyl alcohol **52** and iodobenzene **36**, for example, produced 2-methyl-3-phenylpropanal **53** in 82% yield.



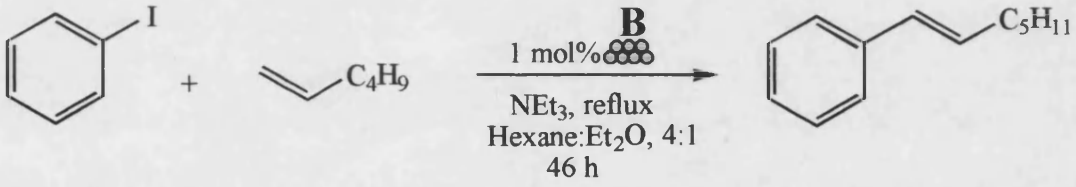
36 **52** **53**

Unfortunately no reaction occurred with beads **A**, **B** or **D** to produce 2-methyl-3-phenyl propanal **53** so at this stage the reaction was studied no further.



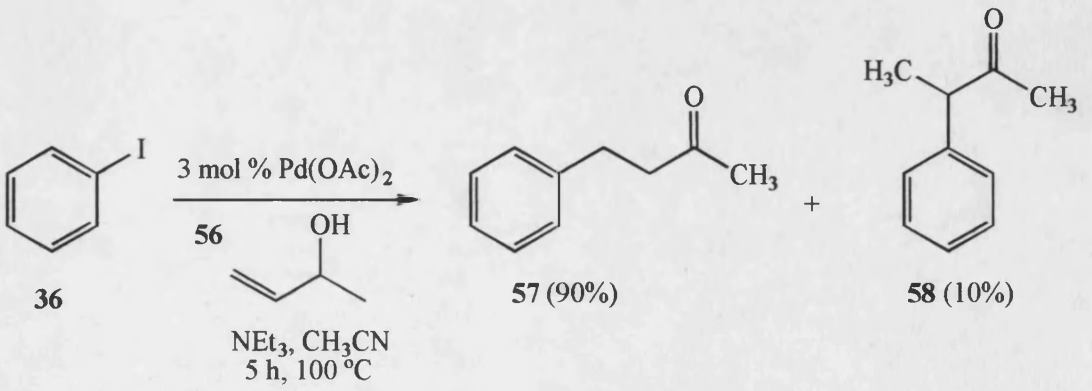
36 **52** **53**

The reaction of iodobenzene **36** with 1-hexene **54** using beads **B** did not only give the desired product **55**, but appeared to produce a mixture of other polymeric and regioisomeric products also. Again, palladium levels for the reaction were minimal (<0.01 mg, <0.1%).



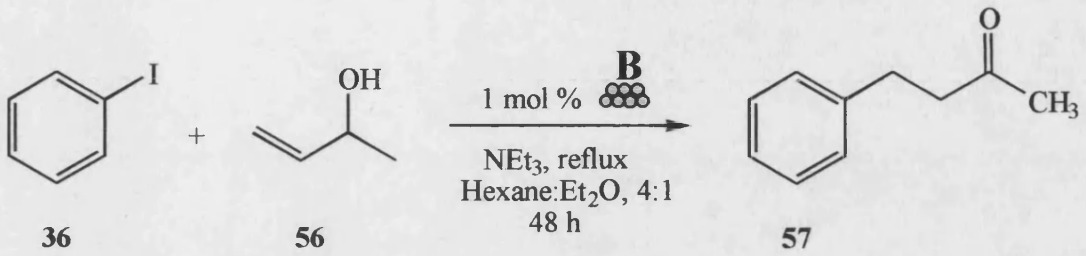
36 **54** **55**

Heck *et al* investigated reactions of the 1-methylated allyl alcohol, 3-buten-2-ol **56**.[116] With iodobenzene **36** as halide source and a palladium acetate catalyst they obtained, in 95.4% yield, a mixture composed of 90% of the terminal 3-phenyl butanone **57** and 10% of the 2-phenyl butanone **58**.



36 **57** (90%) **58** (10%)

The reaction to produce 3-phenyl butanone proved fruitful using beads **B**[117] as illustrated below, to give only the one product **57** (formed as expected, by preferential β-hydride elimination to give the enol, which tautomerises to give the ketone) and no sign of any unsaturated alcoholic by-products.

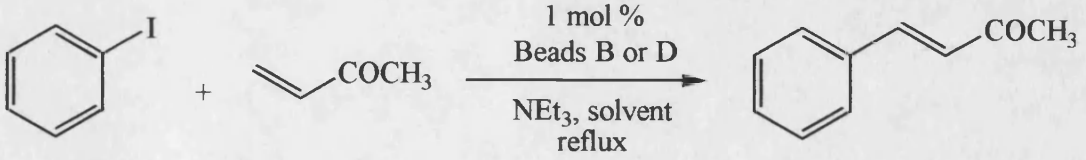


36 **56** **57**

Pd catalyst	Yield (%)	Pd leaching (mg / %)
$PdCl_2$	61	<0.01 mg <0.1%
$Pd(OAc)_2$	88	<0.01 mg <0.1%

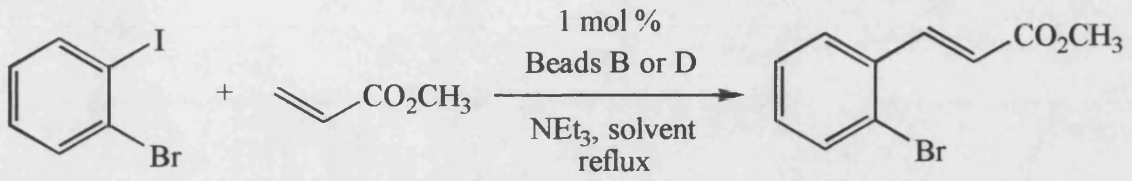
Although the homogeneous catalyst generated product at a faster rate (5 h compared with 48 h) a greater loading of catalyst was employed (3 mol%). The production of a single product was achieved, not a mixture (as in the homogeneous reaction). Palladium leaching was pre-eminent (as illustrated in the table) and very low levels were observed compared with the homogeneous system.

The coupling reaction of methyl vinyl ketone **59** with iodobenzene **36** to give benzalacetone **60** proved unsuccessful using both beads **B** or **D**.



36 **59** **60**

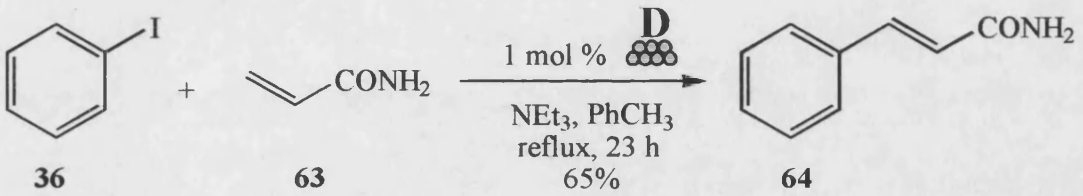
When both bromo and iodo groups are present in the reactants, selective reactions are possible.[118] For example, *p*-bromoiodobenzene **61** reacted with methyl acrylate **49** and a palladium acetate catalyst to form 1-bromo-2-methyl-*trans*-cinnamate **62** in moderate yield (68%). The same reaction performed with beads **B** or **D** gave product in moderate yield but negligible palladium leaching (see table below).



61 **49** **62**

Beads (type)	Pd catalyst	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
B (CPG 239Å)	$PdCl_2$	Hexane:Et_2O 4:1	47	52	<0.01 mg <0.1%
B (CPG 239Å)	$Pd(OAc)_2$	Hexane:Et_2O 4:1	47	59	<0.01 mg <0.1%
-	$PdCl_2$/TPP	Hexane:Et_2O 4:1	28	61	0.33 mg 12.5%
D (Davisil 500Å)	$PdCl_2$	$PhCH_3$	45	56	<0.01 mg 0.3%

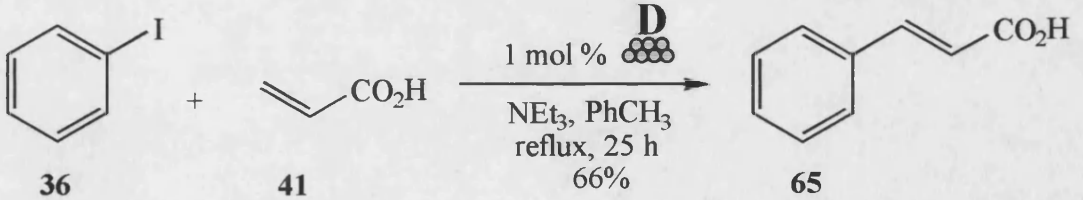
The coupling of acrylamide **63** with iodobenzene **36** proceeded smoothly with beads **D** (containing $PdCl_2$ as catalyst) to give the coupled product **64**. However, no reaction took place with beads **B**. We assumed this was due to the fact that the starting materials were polar and bead **B** complex disintegrated on addition of the acrylamide (high palladium leaching levels were observed). Beads **D** did not contain any ethylene glycol so we assumed that this caused the complications. This reaction has also been performed homogeneously to give high palladium leaching and yields compared favourably with the bead reaction.



36 **63** **64**

Pd leaching <0.01 mg, 0.2%

The coupling of acrylic acid **41** with iodobenzene **36** was successful with beads **D** ($PdCl_2$ as catalyst) but not with beads **B** (again high levels of palladium leaching were observed which was attributed to the more polar supported phase)[67] to give cinnamic acid **65**. The homogeneous reaction was performed to give high palladium leaching and yields that were similar to the bead reaction.

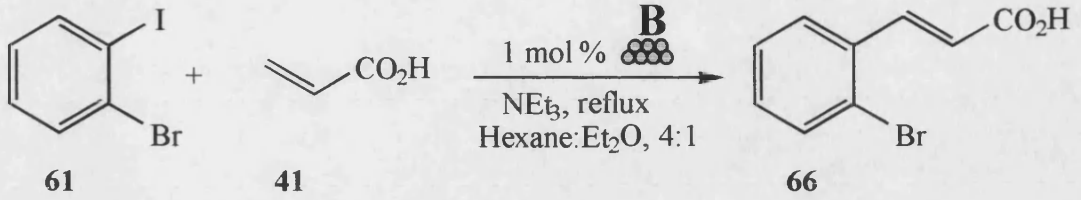


36 **41** **65**

Pd leaching <0.01 mg, 0.3%

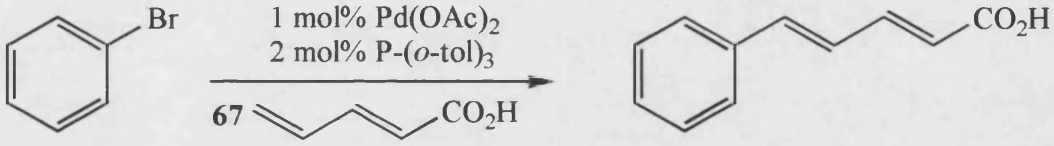
The palladium-catalysed aryl halide reaction with olefins provided a convenient method for the preparation of 1-aryl olefins. Heck *et al* showed that 2-bromoiodobenzene **61** reacted selectively with acrylic acid **41**, 2 equivalents of triethylamine, and a 1 mol% palladium acetate at 100 °C in 1 hour to produce (*E*)-2-bromocinnamic acid **66** in 82% yield.[119]

The preparation of (*E*)-2-bromocinnamic acid **66** was not achieved with beads **B** and was not pursued further due to polarity reasons again.



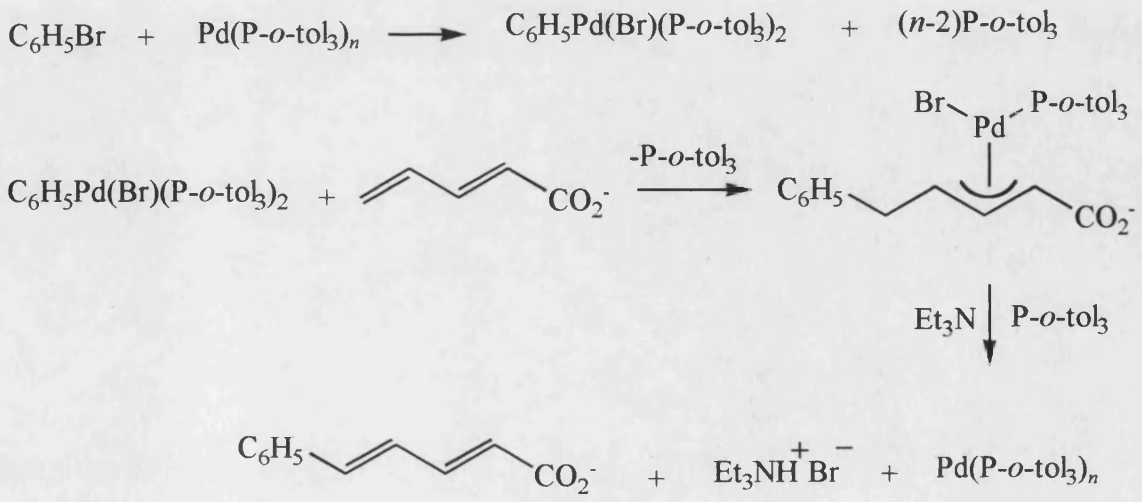
61 **41** **66**

Heck *et al* studied the palladium-catalysed arylation of conjugated dienes to produce arylated dienes.[120] Bromobenzene **51** and the pentadienoic acid **67** reacted to form (*E,E*)-5-phenyl-2,4-pentadienoic acid **68** in 92% (isolated) yield using the standard Heck conditions as outlined below:-



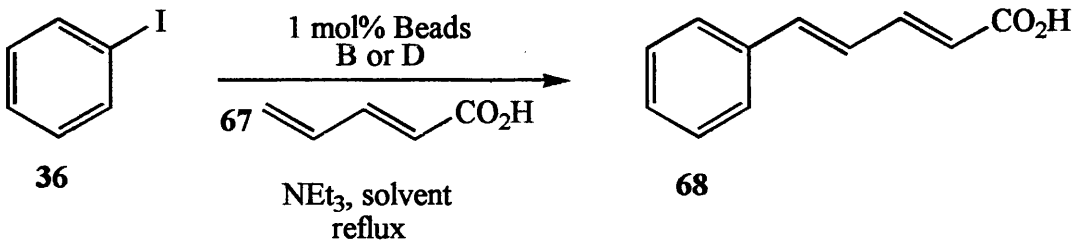
51 NEt_3, 100 °C 92% **68**

It was suggested that a π-allylic palladium (II) intermediate underwent elimination of the palladium hydride because of the activating influence of the neighbouring carboxylate group (**Scheme 13**).



Scheme 13

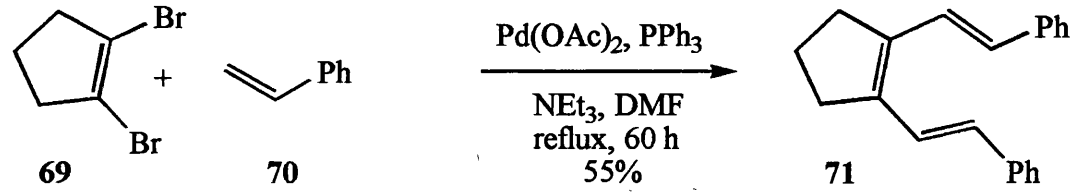
For the reaction we employed iodobenzene **36** as halide source with the pentadienoic acid **67** and performed the reaction using our water-soluble ligand (TPPTS) with beads **B** and **D**, but unfortunately the reaction provided no product.



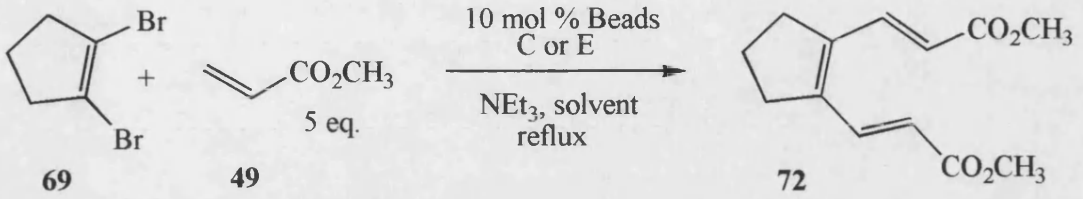
The starting material (*E,E*)-2,4-pentadienoic acid **67** appeared to be too polar for the beads as the complex disintegrated/decomposed on addition of this material. The findings suggested poisoning by the reactants and products by adsorption onto the bead complex. Hence the reaction did not seem to give the desired product using either palladium chloride or palladium acetate as catalyst.

The feasibility of multiple Heck reactions has been instigated by Heck himself.[121] More recently, de Meijere and co-workers have continued the work in this area.[122] They studied the coupling of various 1,2-dibromocycloalkenes with alkenes to give reasonable yields of (*E,Z,E*)-1,3,5-trienes.

For instance, the coupling of 1,2-dibromocyclopentene **69** with styrene **70** afforded the substituted product **71** in reasonable yield. The same group also indicated that the rate was enhanced by applying pressure.[123]



The coupling of 1,2-dibromocyclopentene **69** to methyl acrylate **49** with bead preparations **C** or **E** was investigated using the standard Heck conditions reported by de Meijere to give the coupled product **72**.



69 **49** **72**

Beads (type)	Pd catalyst (0.1 mmol)	Ligand (0.25 mmol)	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C (Davisil 500Å)	$Pd(OAc)_2$	TPPTS	$PhCH_3$	27	69	< 0.01 mg < 0.1%
E (Davisil 300Å)	$Pd(OAc)_2$	TPP	CH_3CN	27	70	0.03 mg 0.3%
-	$Pd(OAc)_2$	TPP	CH_3CN	16	72	3.90 mg 35.8%
-	$Pd(OAc)_2$	TPP	$PhCH_3$	21	70	2.52 mg 23.1%

The results indicated that beads **C** (using the non-polar solvent) gave product in reasonable yield with low palladium leaching. Beads **E** gave similar yields but with more palladium leaching. It was assumed that for the bead **E** preparation an insufficient amount of ligand was added to give the model catalyst and hence some palladium was found in the product.

The bead systems were compared with the homogeneous reaction in terms of metal leaching, yield and reaction time. As envisaged, in the homogeneous system reaction times were shorter but palladium leaching was very high particularly for the more polar solvent, acetonitrile. Yields were analogous for all reactions, hence the bead preparations performed quite remarkably and the results were encouraging.

Conclusions

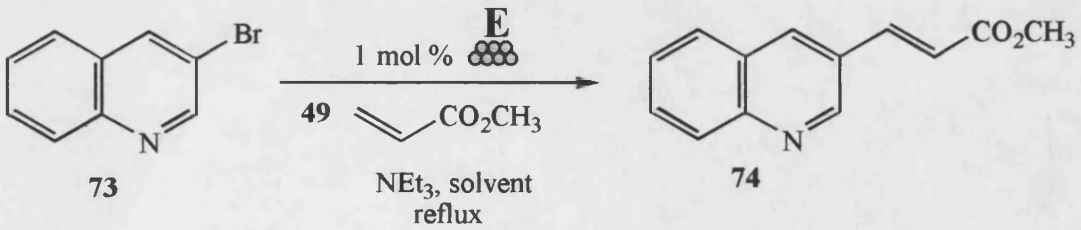
Many of the aforementioned reactions are literature preparations and showed the reaction times for the homogeneous reactions to be much quicker. However, separation proved difficult and leaching of palladium was problematic. The bead preparations proved simple to handle, easy to remove at the end of the reaction and minimal palladium leached into the product (all reactions gave <0.3% of total palladium used in the reaction).

Beads **A**, **B** and **C** were not deemed suitable for use with very polar substrates (such as acrylic acid), since they afforded no product and high levels of palladium leaching, which we attributed to their affinity for the more polar supported phase.

2.7 Heterocyclic Heck reactions using beads C and E

In some of the coupling reactions, significant improvements in yield are often obtained when tri(*o*-tolyl)phosphine is used in place of triphenylphosphine.[124] In order to demonstrate the potential of the new reverse phase beads **E** containing the tri-(*o*-tolyl)phosphine ligand, a number of heterocyclic Heck reactions were investigated.

A sparce number of palladium-catalysed vinylic substitution reactions with heterocyclic bromides have been reported to date.[125] 3-Bromoquinoline **73** reacted in high yield with methyl acrylate **49** using beads **E** to produce the predicted heterocyclic derivative of methyl acrylate **74**. Extremely low levels of palladium leached into the product as illustrated in the table below.

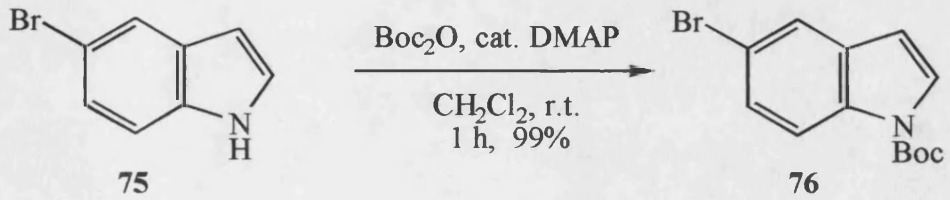


Beads (type)	Pd catalyst (0.01 mmol)	Ligand (0.04 mmol)	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	14	83	< 0.01 mg < 0.1%
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	MeOH	17	81	<0.01 mg <0.1%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	CH_3CN	48	-[a]	0.63 mg 60.6%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	6	84	0.46 mg 44.4%

[a] No yield was recorded as ^1H nmr showed mixture of starting material and product after 48 h so this system was not pursued further.

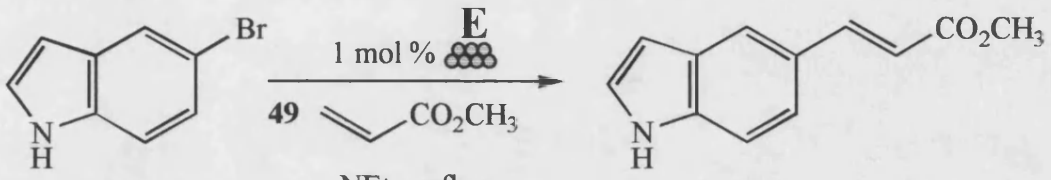
Initial work on the homogeneous system indicated that the solvent played an important factor in the reaction. Acetonitrile proved a poor solvent so the bead reaction was attempted. Hence, the bead reaction was investigated with no solvent and the coupling worked efficiently. The reaction was also successful with the more polar methanol solvent, implying that the reaction without solvent (or methanol) provided an excellent alternative to the homogeneous system. In terms of yield, the two systems (homogeneous and bead) were alike, but beads **E** also maintained palladium levels in the final product at a minimal amount.

In preparation for a coupling reaction, 5-bromoindole was nitrogen protected to see if the reaction and yield would be enhanced.



75 **76**

N-protection of 5-bromoindole **75** was achieved using di-*tert*-butyl carbonate to produce the protected indole **76** in excellent yield as depicted (99%). The N-*tert*-butoxycarbonyl protected bromoindole **76** underwent subsequent coupling with methyl acrylate **49** to give the substituted product **77**. The same reaction was conducted using 5-bromoindole instead. Hence, 5-bromoindole **75** reacted with methyl acrylate **49** to produce **78** in reasonable yields using beads **E** as represented below.

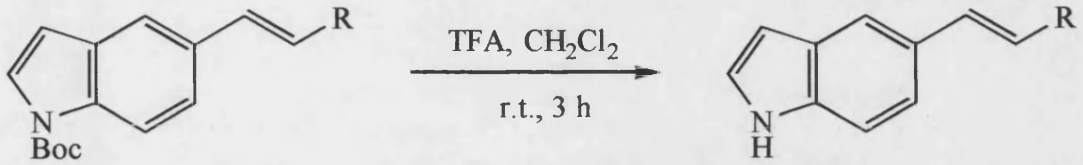


Beads (type)	Pd catalyst (0.01 mmol)	Ligand (0.02 mmol)	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	15	52	< 0.01 mg < 0.1%
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	CH_3CN	17	49	<0.01 mg 0.3%
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none[a]	16	52	<0.01 mg <0.1%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	CH_3CN	6	51	0.38 mg 36.9%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	5	53	0.44 mg 42.1%

[a] Reaction with N-protected indole

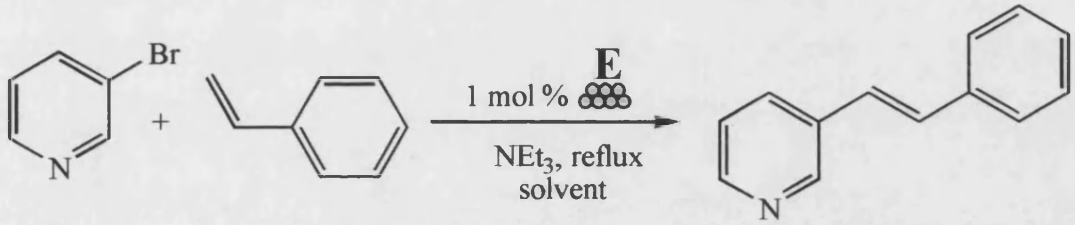
As depicted in the table above, the reaction performed with beads **E** favoured the use of solvent-free conditions. By comparing the homogeneous system with beads **E** it was clear that there was a huge difference in palladium levels and hence the beads were indeed superior.

The crude N-protected indole **77** was deprotected by a simple addition of trifluoroacetic acid to give the product **78** in 52% yield.



77 R = CO_2CH_3 **78**

The coupling of 3-bromopyridine **79** with styrene **70** proved promising with Beads **E** to give good yields of 3-stilbazole **80** and low palladium leaching as outlined below.

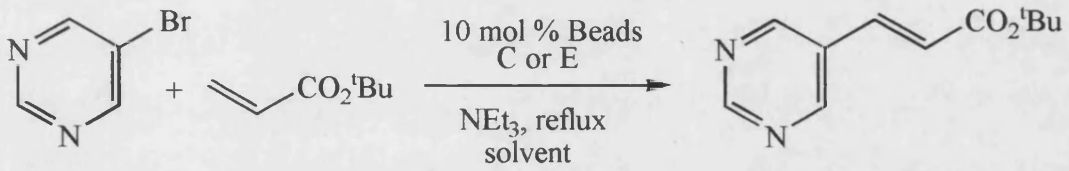


79 **70** **80**

Beads (type)	Pd catalyst (0.01 mmol)	Ligand (0.04 mmol)	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	25	77	< 0.01 mg 0.1%
E (Davisil 300Å)	$Pd(OAc)_2$	P-(*o*-tol)$_3$	CH_3CN	26	77	0.01 mg 1.1%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	CH_3CN	20	78	0.72 mg 69.2%
-	$Pd(OAc)_2$	P-(*o*-tol)$_3$	none	20	77	0.37 mg 35.2%

Again, analogous results were observed when comparing the homogeneous system with beads **E** in the Heck reaction and in the absence of solvent. Once more, high levels of leaching were witnessed for the homogeneous reactions.

Bovy and Rico synthesised β-amino acids with one of the key steps being the use of a Heck coupling between 5-bromopyrimidine **81** and *tert*-butyl acrylate **82**.[126] For the coupling reaction protracted reaction times (72 h) were required to produce *tert*-butyl 3-(5-pyrimidinyl)propenoate **83** and the catalyst was added on two consecutive occasions throughout the reaction. However, in the bead reaction the total palladium loading was added at the beginning of the reaction and it was found that low levels of leaching were observed and yields were comparable with the reaction performed in the literature.



81 **82** **83**

Beads (type)	Pd catalyst (0.10 mmol)	Ligand	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C (Davisil 500Å)	$Pd(OAc)_2$	TPPTS	$PhCH_3$	48	66	< 0.01 mg < 0.1%
E (Davisil 300Å)	$Pd(OAc)_2$	TPP	CH_3CN	52	67	0.56 mg 5.4%
-	$Pd(OAc)_2$	TPP	CH_3CN	68	67	2.82 mg 27.5%
-	$Pd(OAc)_2$	TPP	none	68	67	1.14 mg 11.1%
-	$Pd(OAc)_2$	TPP	$PhCH_3$	68	66	1.14 mg 11.1%

The different method for the reaction using beads **E** is noteworthy as reaction times were reduced and palladium leaching was at least 100-fold less with beads **C**.

Conclusions

The use of the reverse phase system beads provided a new and alternative system which requires expanding for use in other palladium-catalysed reactions. Their use in a few Heck coupling reactions using a polar solvent system with the tri-(*o*-tolyl)phosphine ligand has been explored. Future work may include use of beads **E** in the coupling of the pentadienoic acid with iodobenzene as it is a polar substrate and probably requires the tri-(*o*-tolyl)phosphine ligand.

CHAPTER 3

OTHER PALLADIUM-CATALYSED REACTIONS USING GLASS BEADS

3.1 Introduction

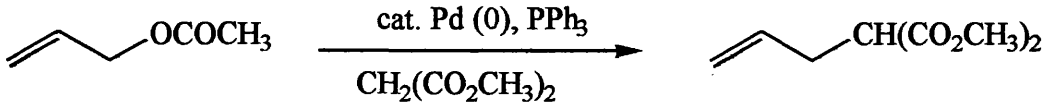
This area of work is split into three sections and illustrates the range and utility of the beads in different palladium-catalysed reactions. Although there are numerous reactions involving the implementation of palladium as catalyst, allylic substitutions, Suzuki couplings and allylic rearrangements have been the main focal point of the work.

3.2 Allylic substitution reactions

3.2.1 Introduction

The palladium catalysed allylic substitution reaction is a very reliable process with new developments in its synthetic utility reported regularly. In 1965, Tsuji *et al* demonstrated a stoichiometric reaction of π-allylpalladium complexes with a range of nucleophiles to effect the overall substitution.[127] Throughout the early 1970's the allylic substitution reaction was developed into a catalytic process and use of palladium as catalyst provided the most coverage to date.[128]

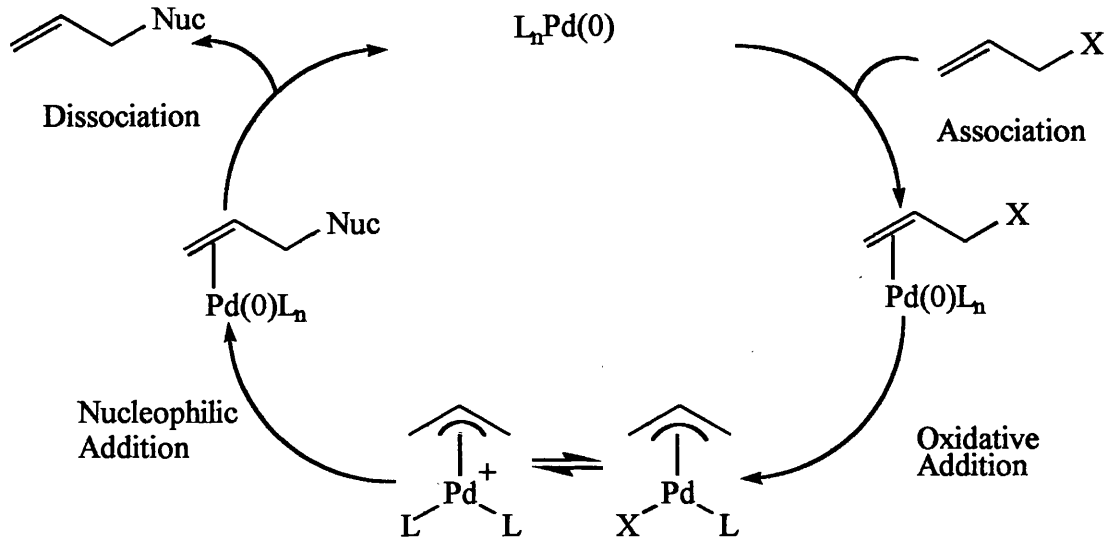
Palladium catalysed allylic substitution is a versatile process encompassing a wide range of allyl systems and their nucleophilic partners. Some of the work in this area has been pioneered within the group.[129] Our group has also shown some of the applications of this chemistry to synthesise α-[130] and β-amino acids[131] for use by the pharmaceutical industry. The basic palladium catalysed allylic substitution process involves the conversion of a suitable allylic substrate, such as an allyl acetate, into its substitution product through reaction with a nucleophile (dimethyl malonate) in the presence of catalytic amounts of phosphine ligand and palladium (0) (**Scheme 14**).



Scheme 14

3.2.2 Mechanism

The mechanism for the reaction is outlined in **Scheme 15**. Initial association of a palladium (0) catalyst with an alkene, followed by an oxidative addition process affords a π-allylpalladium intermediate (η^3-allyl complex). In the presence of a phosphine, an equilibrium between a neutral and cationic complex results. The cationic complex is favoured by the use of bidentate phosphine ligands. These complexes behave as palladium stabilised allyl cations, which readily undergo reaction with various nucleophiles to afford a palladium (0) complex of product. Dissociation of the palladium (0) liberates the product and regenerates the active palladium catalyst.



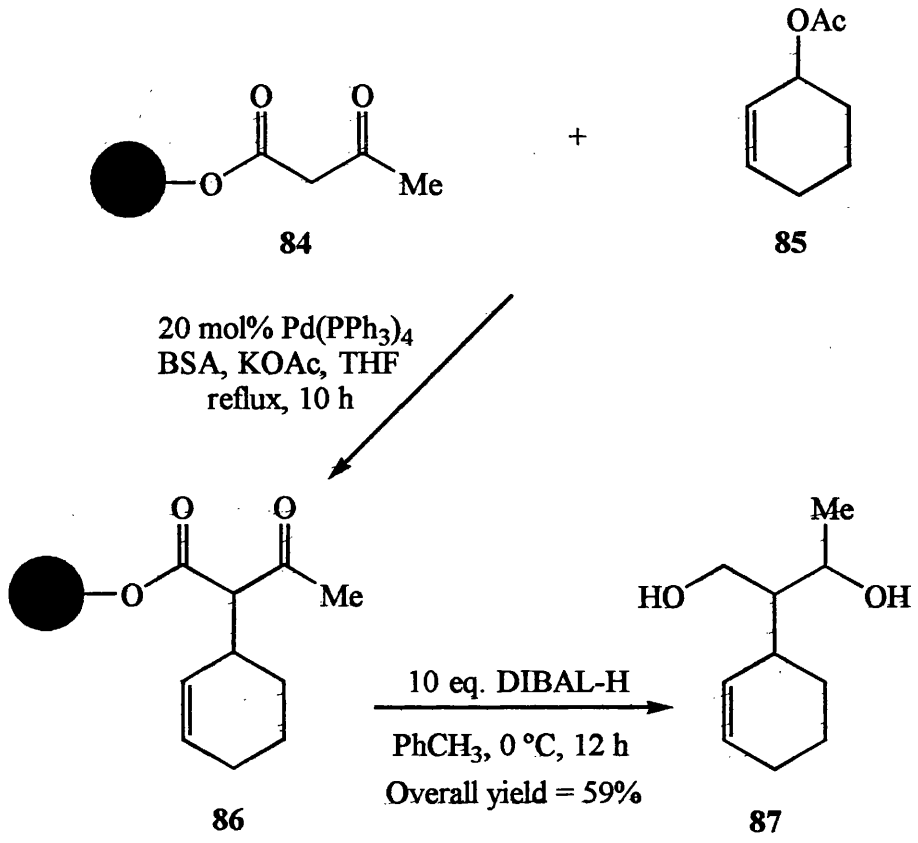
Scheme 15

3.2.3 Solid supports in allylic substitution reactions

Solid supports attached to substrates

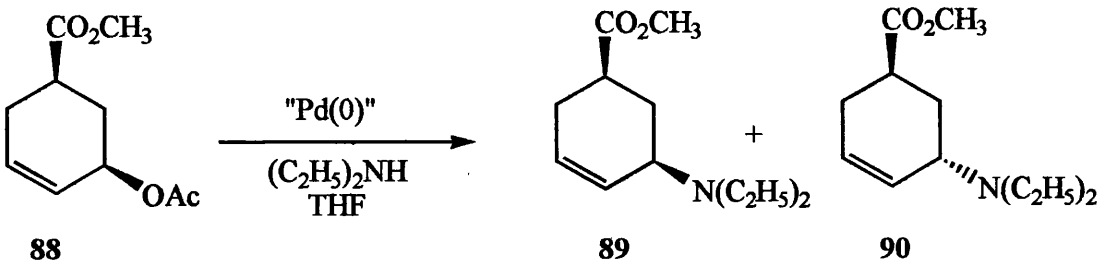
Scant attention has been paid in this area, although this is being developed within our group. Use of polymer-bound 1,3-dicarbonyl compounds in palladium (0)-catalysed allylic substitution reactions has been reported by Tietze *et al.*[132] They synthesised various resin-linked 1,3-dicarbonyl compounds and reacted them with many sterically less hindered allylic substrates to give dialkylated products and built up combinatorial libraries. Selective monoalkylation was achieved using the more sterically hindered cyclic allylic acetates.

Thus, 2-cyclohexenyl acetate **85** was reacted with polymer-bound acetoacetate **84** using a high loading of palladium catalyst and standard conditions to give the substituted product **86**, which after reductive cleavage gave the diol **87**.



Solid supports attached to palladium catalysts

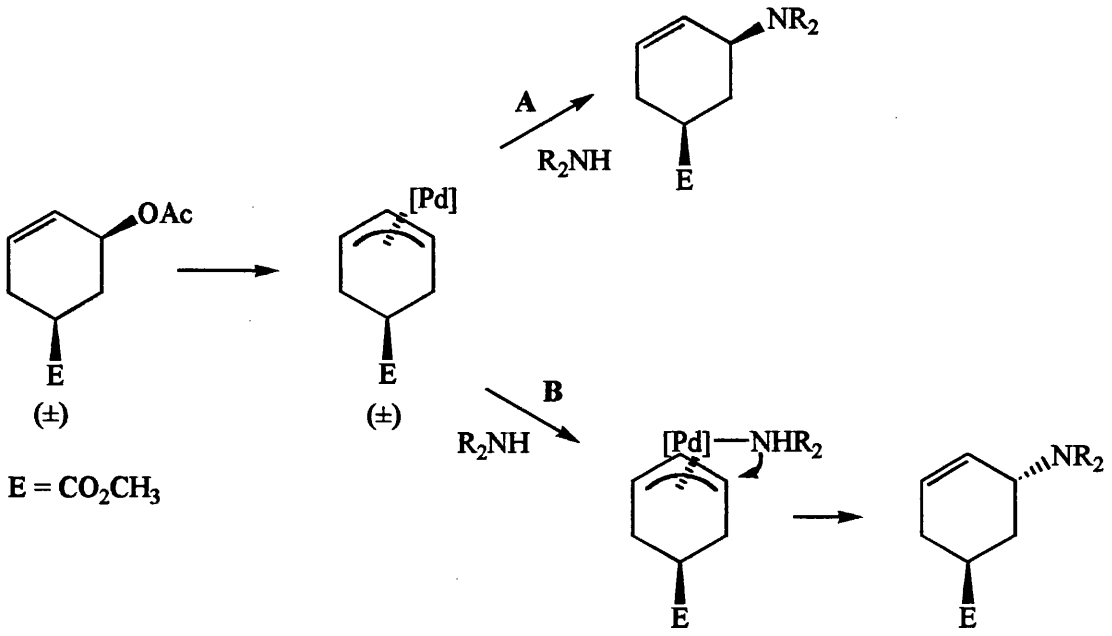
As early as 1978, work had been investigated by Trost and Keinan on supporting a palladium (0) species on both silica gel and cross-linked polystyrene for implementation into allylic alkylation reactions.[133] Both phosphinylated silica gel and phosphinylated polystyrene were subjected to palladation to form the desired catalyst. On treatment of the cyclic acetate **88** with diethylamine and the soluble palladium catalyst (either on polystyrene or silica gel as support) they noticed that one isomer was preferentially formed (**89** rather than **90**).



88 **89** **90**

Palladium (0) source	Amount of each isomer		Yield (%)
$(Ph_3P)_4Pd$	67	33	85
Polystyrene catalyst	100	0	83
Silica gel catalyst	100	0	72

They proposed the crossover resulted from a mixed mechanism (**Scheme 16**) in which the nucleophile attacked carbon directly, to give the product **89** of net retention of configuration (**Path A**). Alternatively, reductive elimination of the palladium intermediate gave the product **90** of inverted configuration with respect to the starting acetate **88** (**Path B**).

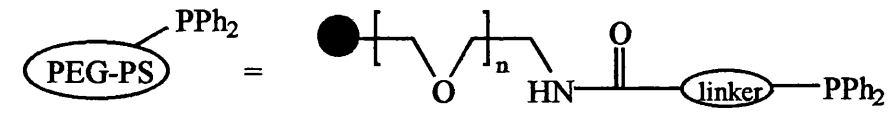


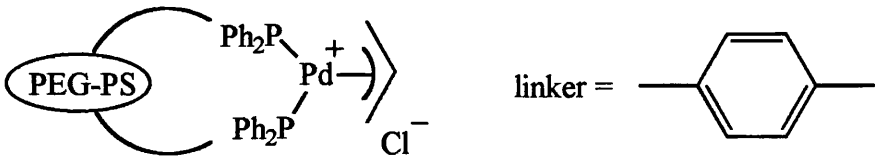
Scheme 16

If the palladium in the π-allyl complex was bound to a polymer, which should effectively shield the metal from coordinating with the nucleophile, **path B** should be excluded. Indeed this was the case in these reactions and hence, both types of polymer bound catalysts showed complete stereospecificity.

Bergbreiter and Lui accounted work on allylic substitution with a water-soluble polymer-bound catalyst in aqueous or biphasic media to give a high activity catalyst which could also be recycled.[134] They synthesised polymer-bound palladium (0)-phosphine catalysts based on the water-soluble polymer poly (*N*-isopropyl)acrylamide (PNIPAM). PNIPAM was known to possess good solubility in water or mixed aqueous solvents.

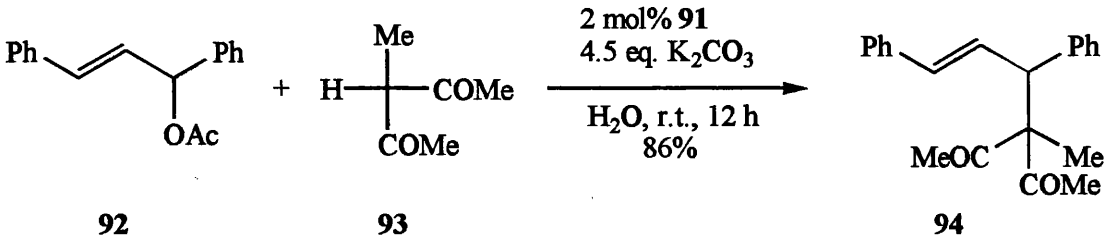
Allylic substitution of allyl acetates with a range of nucleophiles mediated by an amphiphilic polymer-bound palladium complex **91** has been carried out by Uozumi and co-workers.[135] The catalyst was prepared from Tentagel in two high-yielding steps; owing to the presence of PEG residues in the polymer backbone, the catalyst displayed excellent swelling properties in water.





91

A representative example for alkylation used 1,3-diphenyl-prop-2-enyl acetate **92** as the model substrate, in the presence of 3-methyl-2,4-pentadione **93** as nucleophile and potassium carbonate (4.5 equiv.) as base. The reaction took place in water, to give the substituted product **94**. The catalyst could be re-used six times without loss in activity, which coupled with water as the solvent, represents an environmentally friendly protocol.



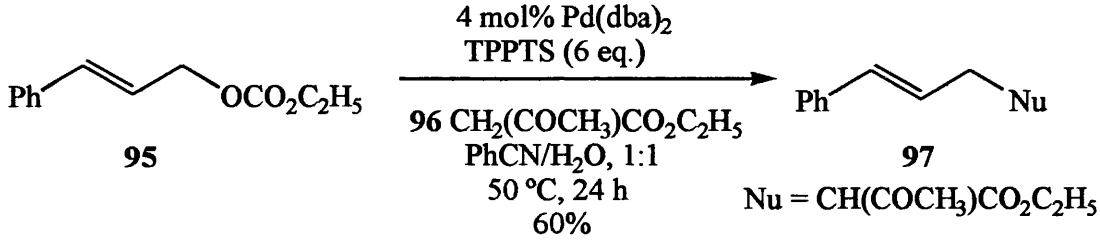
92 **93** **94**

Choplin *et al* have used palladium (0) stabilised by phosphines as catalysts for the allylic alkylation reaction.[136] The catalyst was "immobilised" in water (after substitution of the triphenylphosphine ligands by the trisodium salt of the tri(sulfonatedphenyl)phosphine (TPPTS)) and used under biphasic water/nitrile conditions. They tested the potential of the supported aqueous phase catalysis (SAPC) by attaching the water-soluble catalyst onto a silica support. More recently, we have demonstrated the use of glass bead technology for palladium-catalysed allylic substitution reactions.[117]

However, this year Choplin *et al* updated their findings by publishing optimum working conditions for the silica-supported catalyst.[137] They concluded the following observations from their studies. Choice of nitrile as solvent proved interesting; acetonitrile showed lower activity than the biphasic system but benzonitrile gave superior results to the biphasic analog for both nucleophiles regardless of the water content. This phenomenon was correlated to a large enhancement of the interphase surface area thus the latter solvent was used. Maximum activity was observed with water content close to *ca.* 50% wt. water (close to that necessary to fill the pores of the silica support). An adequate amount of water was required to ensure mobility of the catalyst, but too much allowed for the formation of cinnamyl alcohol (from cinnamyl ethyl carbonate as substrate) as by-product, palladium and water leaching. Finally, the SAP catalyst was, in all cases, more stable towards degradation to metallic particles.

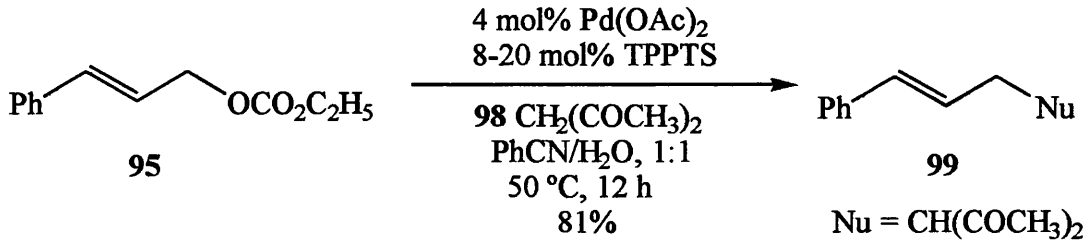
3.2.4 Water-soluble ligands in allylic substitution reactions

Allylic substitution reactions have previously been reported using a two phase system with a palladium catalyst and TPPTS as the ligand, allowing easy recovery and recycling of the catalyst.[138] The reaction between the allylic substrate and the nucleophile was carried out in an aqueous-organic medium and the reaction was complete after a few hours at 50 °C. For instance, the active methylene compound ethyl acetoacetate **96** reacted with cinnamyl ethyl carbonate **95** in benzonitrile as organic solvent to form one single regio- and stereoisomer **97** with the *(E)*- configuration.



The catalyst was recycled and the same reaction performed again. For the above reaction a slight decrease in yield was observed after 4 recycles (45% yield). The same group investigated organic co-solvents like ethers but rapid decomposition of the palladium catalyst occurred.

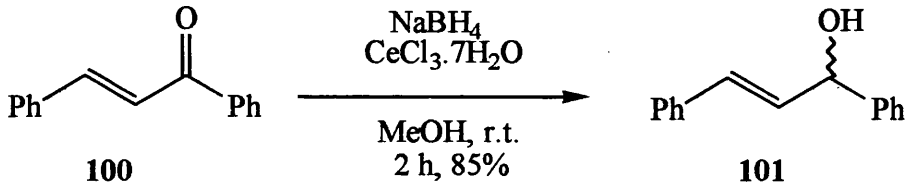
Another example of this type of reaction was described by Blart *et al.*[139] They observed that the use of palladium acetate in combination with TPPTS provided an excellent catalyst for allylic substitution in an organic-aqueous medium, the organic solvent used being a nitrile.[101] One such reaction reported the allylic substitution of *(E)*-cinnamyl ethyl carbonate **95** with acetylacetone **98** to give a single regio- and stereoisomer **99** with the *(E)*- configuration in good yield.



3.2.5 Allylic substitution reactions using beads C and D

Although a vast range of nucleophiles has been employed in the allylic substitution reaction, we only performed work with the "soft" stabilised enolate of dimethyl malonate.

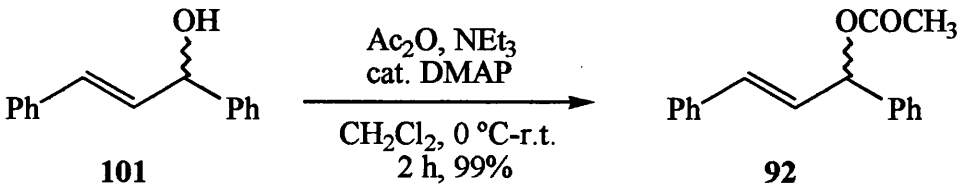
(*E*)-1,3-Diphenyl-1-acetoxy-prop-2-ene, **92** was generated in two steps from commercially available chalcone **100**. Treatment of chalcone **100** with sodium borohydride resulted in the formation of the disubstituted allylic alcohol **101** in good yield.



100 **101**

^{1}H NMR analysis of **101** confirmed product formation with the appearance of a one proton broad singlet at δ 2.5 ppm, corresponding to the proton of the hydroxy group.

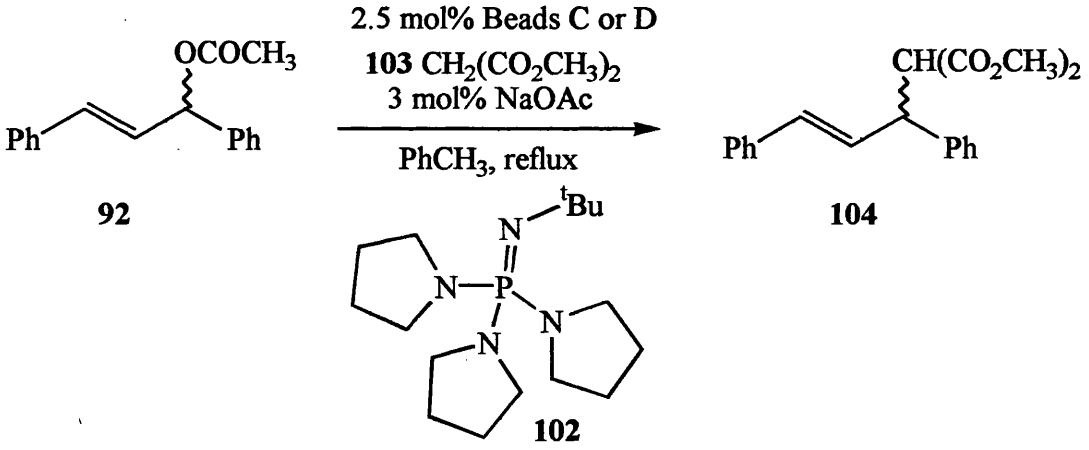
Acetylation of the allylic alcohol **101** was achieved using acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP in dichloromethane at room temperature. ^{1}H NMR analysis of **92** confirmed product formation with the disappearance of a one proton broad singlet at δ 2.5 ppm, corresponding to the hydroxy group of **101** and the appearance of a three proton singlet at δ 2.1 ppm, corresponding to the protons of the acetoxy group.



101 **92**

The palladium catalysed allylic substitution reactions were performed on beads **C** and **D** and compared with the homogeneous system in terms of reaction time, yield and palladium leaching. We opted for a phosphazene base **102** to deprotonate dimethyl malonate **103**, since we reasoned that the resultant active nucleophile would still prefer to reside in the bulk organic layer. In all cases palladium chloride or palladium acetate and TPPTS were employed in the construction of the bead complex with the same amount of ethylene glycol as employed in the Heck reactions.

A solution of phosphazene base **102**, dimethyl malonate **103** and sodium acetate in toluene was added to a stirred solution of the allylic acetate **92**, beads **C** or **D** (containing 2.5 mol% palladium catalyst) which had been pre-stirred for 15 minutes in toluene at room temperature. The reaction was heated to reflux until the alkylated product **104** was formed and as shown in the results, the product was isolated in reasonable yield.

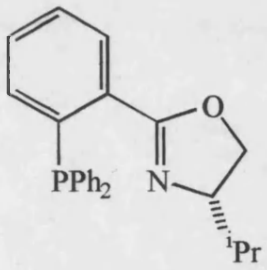


92 **104** **102**

In every case ^{1}H NMR analysis confirmed product formation with the disappearance of a three proton singlet at δ 2.1 ppm, corresponding to the acetoxy group of **92** and the appearance of a one proton doublet at δ 4.0 ppm corresponding to the methine proton of **104**.

Beads	Pd catalyst	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$Pd(OAc)_2$	$PhCH_3$	120	51	<0.01 mg <0.1%
D	$Pd(OAc)_2$	$PhCH_3$	120	43	<0.01 mg 0.3%
D	$PdCl_2$	$PhCH_3$	120	32	<0.01 mg 0.2%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$PhCH_3$	18	91	0.23 mg 9.8%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	THF	12	92	0.51 mg 21.9%

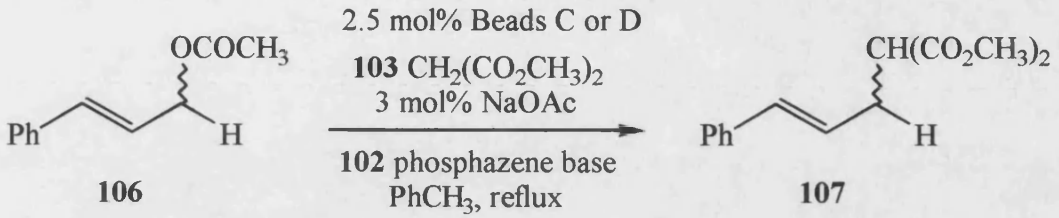
For the homogeneous system we employed BSA as the base, the phosphinooxazoline **105** as ligand (10 mol%), allyl palladium chloride dimer (2.5 mol%) as catalyst, and tried THF and toluene as solvents. Toluene was used so a direct comparison could be made with our bead catalysts.



105

By looking at the results we can unfortunately conclude that the bead systems tried (**C** and **D**) are not comparable with the homogeneous system in terms of yield or reaction time. Palladium levels are high in the homogeneous reactions though. Beads **C** (using palladium acetate as catalyst) gave the best results of the two bead systems overall.

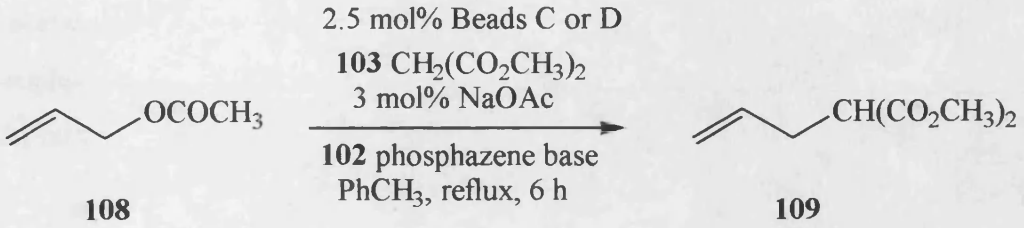
To cinnamyl acetate **106**, the nucleophilic substitution reaction occurred with dimethyl malonate **103** as nucleophile to produce the substituted product **107** in excellent yield using beads **C** and **D**. Again a comparison between the homogeneous and bead system was made (see results table).



Beads	Pd catalyst	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$Pd(OAc)_2$	$PhCH_3$	48	92	<0.01 mg <0.1%
D	$Pd(OAc)_2$	$PhCH_3$	48	61	<0.01 mg 0.3%
D	$PdCl_2$	$PhCH_3$	48	34	<0.01 mg 0.2%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$PhCH_3$	52	92	0.20 mg 8.7%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	THF	48	93	0.35 mg 15.0%

By comparing the results we can observe that beads **C** gave similar results to the homogeneous system in terms of yield and reaction time except the beads gave over a ten fold reduction on palladium leaching and hence the beads offered an added advantage. Beads **D** proved poor in comparison with beads **C** as a catalyst in every way. For beads **D** the catalyst made with palladium chloride seemed inadequate as very poor reactivity was observed throughout the experiments.

The methodology was further exemplified by a reaction involving allyl acetate **108** with malonate **103** as nucleophile to give the resulting substitution product **109** in reasonable yields in the case of beads **C**. ^1H NMR analysis confirmed the correct product by presence of one proton corresponding to a triplet indicative of the methine in the product **109**.

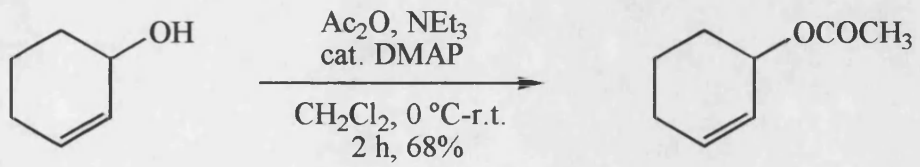


108 **109**

Beads	Pd catalyst	Solvent	Yield (%)	Pd leaching (mg / %)
C	$Pd(OAc)_2$	$PhCH_3$	59	<0.01 mg <0.1%
D	$Pd(OAc)_2$	$PhCH_3$	33	<0.01 mg 0.2%
D	$PdCl_2$	$PhCH_3$	28	<0.01 mg 0.2%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$PhCH_3$	64	0.21 mg 9.2%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	THF	68	0.40 mg 17.1%

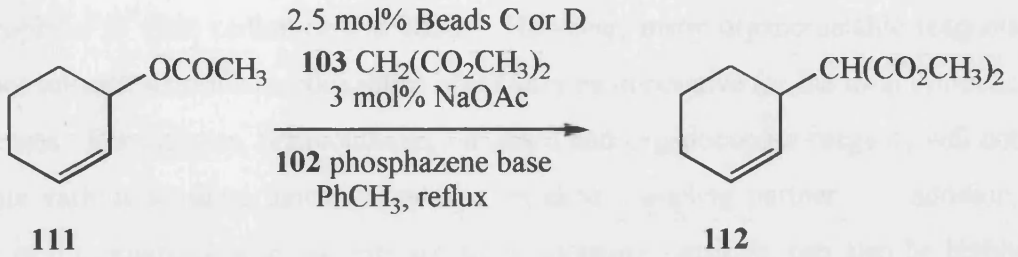
The results show that again beads **C** are analogous to the homogeneous system in activity but obviously have the added bonus that they maintain palladium leaching at a lower level in the final product which is a vital asset.

Another substrate was synthesised for the palladium catalysed allylic substitution reaction. Acetylation of 2-cyclohexen-1-ol **110** was achieved using acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP in dichloromethane at room temperature. ^{1}H NMR analysis of **111** confirmed product formation with the appearance of the three proton singlet at δ 2.2 ppm, corresponding to the protons of the acetoxy group.



110 **111**

The acetate **111** was converted into the alkylated product with use of the malonate **103** nucleophile to give the substituted product **112** in moderate yield as indicated in the results table.



111 **112**

Beads	Pd catalyst	Solvent	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$Pd(OAc)_2$	$PhCH_3$	16	59	<0.01 mg <0.1%
D	$Pd(OAc)_2$	$PhCH_3$	24	49	<0.01 mg 0.2%
D	$PdCl_2$	$PhCH_3$	24	42	<0.01 mg 0.3%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	$PhCH_3$	24	58	0.22 mg 9.4%
-	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	THF	24	60	0.37 mg 16.0%

As shown throughout the work in this area beads **C** are analogous to the homogeneous system in terms of activity and yield but palladium levels are drastically reduced with the beads. Beads **D** are inferior to beads **C**.

Conclusion

We have shown that the allylic substitution reaction works with beads **C** and **D** but better results are ascertained with **C**. The allyl acetates **92**, **106**, **108** and **111** were successfully converted into the corresponding allylic substitution products **104**, **107**, **109** and **112** with reasonable yields and with consistently low levels of palladium leaching. Future work would involve designing suitable chiral water-soluble ligands for implementation in the allylic substitution reaction to synthesise enantiomerically enriched products.

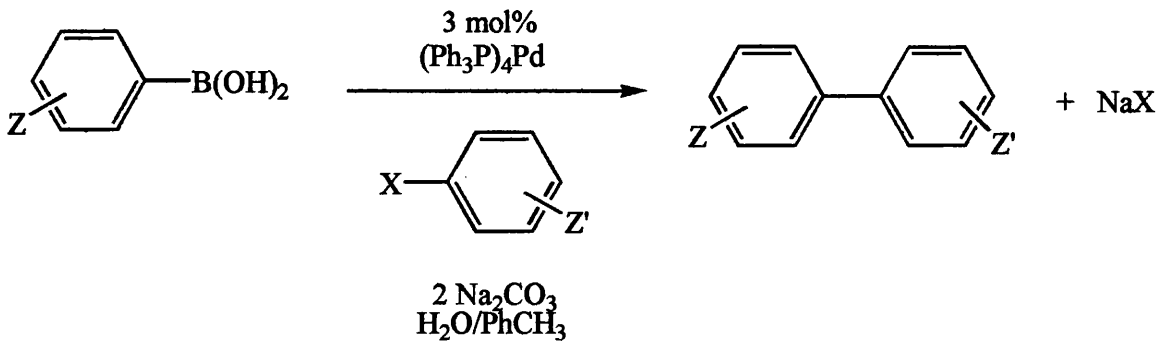
3.3 Suzuki Coupling reactions

3.3.1 Introduction

During the last two decades there have been rapid developments in palladium-catalysed cross-couplings of organometallics (Mg, Li, Cu, Zn, Zr, Al, Sn and B) with organic electrophiles to form carbon-carbon bonds. However, many organometallic reagents will not tolerate sensitive functionalities which may be imperative for the total synthetic sequences. For instance, organolithium, Grignard and organocopper reagents will not tolerate various sensitive functional groups on either coupling partner. In addition, some of the organometallic reagents are air or moisture sensitive, can also be highly toxic or arduous to prepare, and few can be purified and stored.

However, arene- and alkene-boronic acids, on the other hand, which are air-stable materials of relatively low toxicity, are one of the few organometallic classes which will undergo the Suzuki reaction in the presence of a wide range of functional groups. Use of boron as part of the organometallic species has become increasingly popular since; **(1)** it is compatible with the presence of electrophilic functional groups; **(2)** many boron compounds are stable; **(3)** several arylboronic acids are commercially available; **(4)** the inorganic product of the reaction can be easily eliminated in water, and; **(5)** the reaction conditions tolerate aqueous media, which renders elimination of the boron-containing reaction products easier.

The discovery that arylboronic acids undergo palladium-catalysed cross-coupling with aryl halides in the presence of a base has stimulated enormous interest in the application of the Suzuki reaction,[140] and variants developed subsequently, to the synthesis of unsymmetrical biaryls and related compounds as shown in **Scheme 17**.

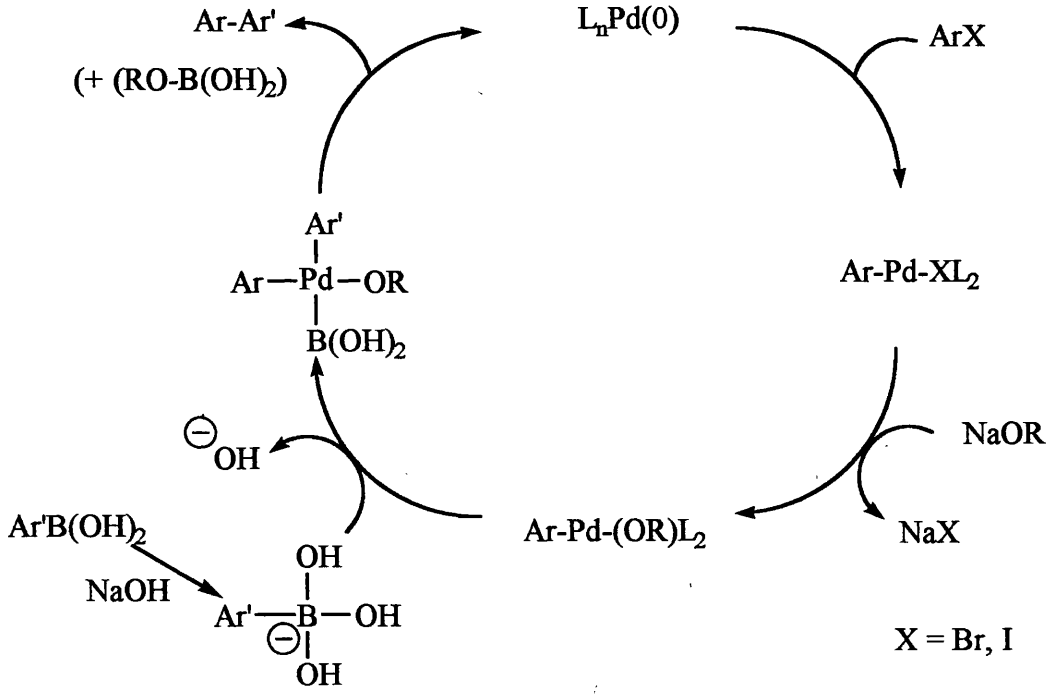


Scheme 17

Palladium catalysed cross-coupling reactions of aryl halides or triflates with boronic acids (commonly referred to as the Suzuki reaction) is a powerful, versatile and popular tool for selective construction of carbon-carbon bonds and has been widely published. Suzuki *et al*[141] pioneered much of the work in this area and have reported several cross-couplings between alkenylboranes and organic halides such as alkenyl,[142] alkynyl,[142] aryl,[143] allyl[144] and benzyl[144] halides catalysed by a catalytic amount of tetrakis (triphenylphosphine) palladium, $Pd(PPh_3)_4$ in the presence of a suitable base.

3.3.2 Mechanism

Suzuki proposed a widely accepted catalytic cycle for the mechanism of the reaction.[145] The cycle is initiated by the oxidative addition of the organic halide to the stabilised Pd (0) species (**Scheme 18**).



Scheme 18

The transmetallation step transfers the Ar' group from the metal boron to the metal palladium to generate an intermediate containing Ar, Ar', $B(OH)_2$, and OR in the coordination sphere of palladium. Two reductive eliminations from this intermediate produce the coupled Ar-Ar' product and the final boric acid derivative.

In its general trends the cycle is similar to other cycles proposed for cross-couplings induced by other metals such as Sn, Mg or Zn. The difference is the inclusion of a step in which a base RO- is introduced in the coordination sphere of Pd to give an organopalladium alkoxide (R-Pd-OR) or organopalladium hydroxide (R-Pd-OH) depending on the base used. These organopalladium alkoxides or organopalladium hydroxides are believed to be more reactive than the organopalladium halide.

As shown in **Scheme 18**, two equivalents of base are required in this catalytic cycle. One equivalent is utilised in the formation of boronate, which is consistent with the fact that boronic acids act as acids in the Lewis sense, with the formation of a tetravalent boron atom. The anionic nature of the organic group in organoboronic acids is expected to be enhanced by the formation of an organoborate. The second equivalent of base is consumed in the metathetical displacement to form organopalladium hydroxide. The organopalladium hydroxide (or alkoxide) should be more reactive than the organopalladium halide, since the Pd-O bond is more polar than the Pd-Br bond, owing to greater electronegativity of oxygen relative to bromine. The transmetallation reaction is favoured by the formation of both the arylboronate and the organopalladium hydroxide (or alkoxide).

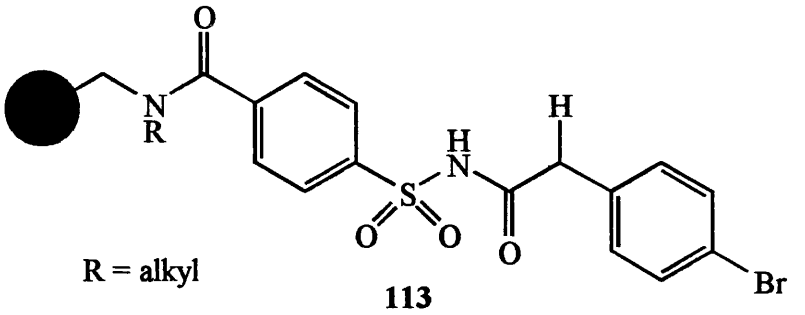
Hence, the presence of mineral base seems to be fundamental for the success of the Suzuki-type cross-coupling, which makes boron-based couplings different from those based on the other three metals.[146] It has been suggested that the fundamental role of the mineral base is in the transmetalation step which occurs on a $[Ar'B(OH)_3]^-$ species rather than on the arylboronic acid.[147] In any case, the presence of mineral base seems to be essential. It should be noted that some steps of the proposed Suzuki coupling mechanism have not been fully characterised.

3.3.3 Solid supports in Suzuki coupling reactions

Solid supports attached to substrates

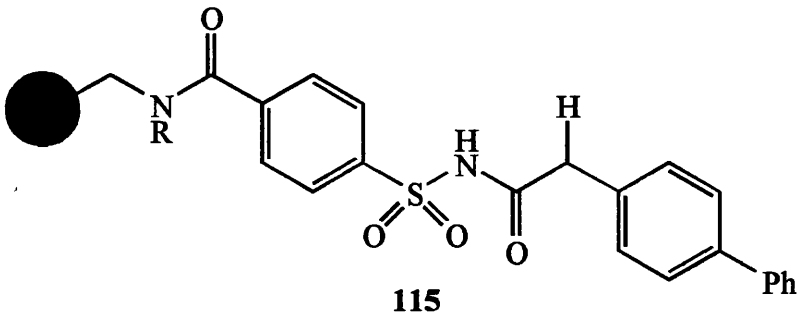
Backes and Ellman synthesised a series of phenylacetic acid derivatives on supports by enolate alkylation and subsequent Suzuki reaction.[148] The rarely used safety-catch linker was employed since it is stable under the chosen reaction conditions. For the palladium-catalysed Suzuki reaction, a series of either aryl boronic acids or alkylboranes produced by *in situ* hydroboration of alkenes served as coupling partners.

In a typical example, the supported acylsulfonamide **113** was coupled to phenylboronic acid **114** using standard Suzuki reaction conditions to give the coupled product **115** in good yield. They noted that performing the reaction in dimethoxyethane as solvent, led to the precipitation of Pd (0), which could greatly implicate the subsequent synthetic steps.



113

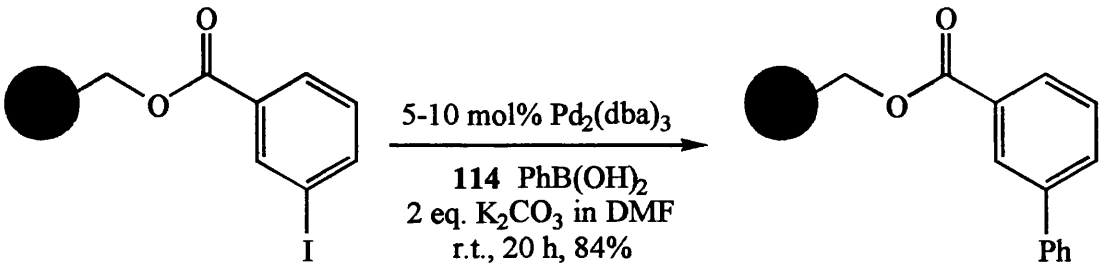
cat. $Pd(PPh_3)_4$
2M Na_2CO_3, **114** $PhB(OH)_2$
THF, 65 °C
24-40 h
93% after cleavage



115

The palladium-catalysed cross-coupling reaction was performed by Frenette and Friesen who attached Merrifield resin to aryl bromides or iodides and carried out Suzuki reactions using "standard" conditions.[149] Another group used the Merrifield resin to form various biphenyltetrazole derivatives which may have potential use in the development of angiotensin II receptor antagonists.

Guiles *et al* have also reported use of a polymer-supported substrate to perform organoboron couplings.[150] They coupled the Wang resin supported iodobenzoic acid **116** with phenylboronic acid **114** at room temperature and a Pd (0) catalyst to give the product **117** after 20 hours. Bromo-substituted benzoate analogues were found to be completely unreactive under similar reaction conditions.



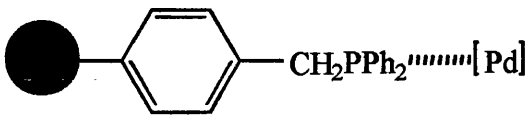
116 **117**

A rapidly expanding type of chemistry involves the use of microwave assisted reactions. This is particularly useful in combinatorial chemistry where reaction times and reaction temperatures are of utmost importance. Thus, Hallberg and co-workers have investigated the application of microwave irradiation in Suzuki coupling reactions to enhance reaction rates and this method provided an efficient procedure.[151] No doubt there will be many more developments in this area.

Solid supports attached to palladium catalysts

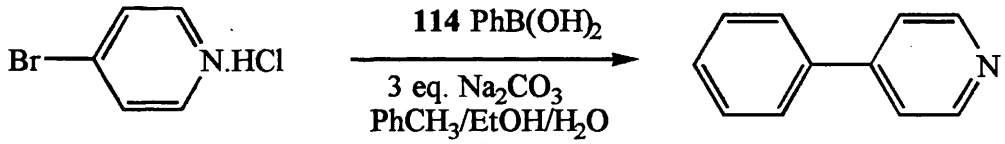
There has been a sparce amount of literature on supported palladium catalysts for use directly in the Suzuki coupling reaction. Recently, Jang has investigated the use of polymer-supported palladium as a catalyst for efficient Suzuki cross-coupling reactions of organoboron reagents with alkyl and aryl- triflates and halides.[152]

More recently, Fenger and Drian described the use of a polymer-supported catalyst to react boronic acid with various bromoaromatics.[153] They based the catalyst on triphenylphosphine and synthesised a diphenylphosphinated DVB-crosslinked polystyrene catalyst **118** for implementation in several cross-coupling reactions.



118

They performed the coupling of phenylboronic acid **114** with 4-bromopyridine **119** using several different variations of catalyst to give the substituted product **120**. The most active catalysts were obtained with $Pd(PPh_3)_4$ and an example of a reaction with this catalyst is illustrated below:-



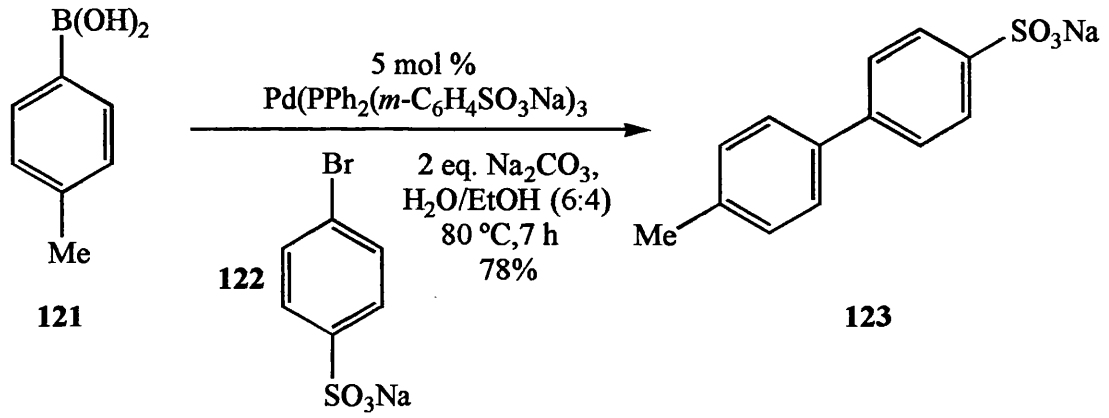
119 **120**

They also tested for precious metal leaching from the support and found that using the same loading of catalyst as shown in the above reaction, only 0.60-0.65% of the initial amount of palladium was lost (*ca.* 0.06 mol%)

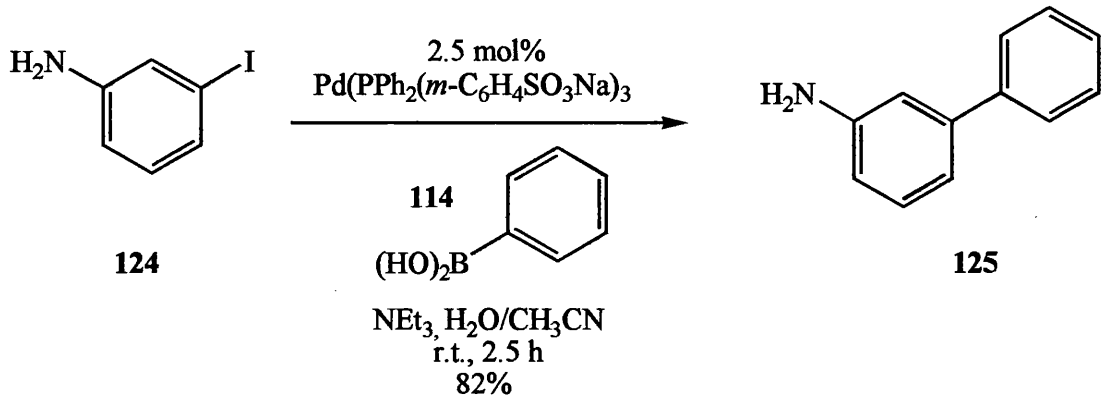
3.3.4 Water-soluble ligands in Suzuki coupling reactions

A substantial amount of work has been performed on Suzuki coupling reactions possibly because water is already used as part of a two-phase reaction medium where the catalyst and organic halide reside in the organic phase.[154] We have reviewed recent progress in this area using our hydrophilic catalyst system.[69]

Casalnuovo and Calabrese reported that the water-soluble Pd (0) complex Pd [($PPh_2(m\text{-}C_6H_4SO_3M)_3$] (M=$Na^+$, K^+) catalysed the cross-coupling of highly lipophobic sodium *p*-bromobenzenesulfonate **122** with *p*-methylbenzeneboronic acid **121** to give the coupled product **123** in good yield (78%) compared with a poor yield (36%) catalysed by $Pd(PPh_3)_4$ as shown below:-[100b]



Genêt *et al* have reported the use of the Suzuki coupling reaction to synthesise substituted arenes and ethynyl alkenes using a palladium (0) water-soluble catalyst.[101] For instance, phenylboronic acid **114** was coupled in an aqueous medium with aryl iodide **124** giving the coupled product **125** in good yield. Genêt and co-workers have also demonstrated the use of the same catalyst system in the synthesis of functionalised dienes and employed diisopropylamine as base.

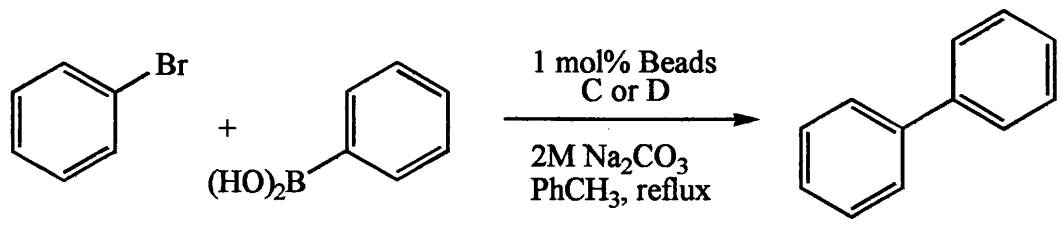


Palladium-catalysed cross-coupling reactions of arylboronic acids and esters with aryl halides and water as solvent has been exemplified by Beletskaya *et al.*[155] They noted that reactions with simple palladium salts and bases such as sodium hydroxide/carbonate or potassium carbonate/phosphate gave the optimal reaction conditions and reactions were counterproductive when palladium complexes with phosphine ligands were tried. However, for water-insoluble substrates it was deemed necessary to use a DMF-water mixture with high DMF content (from 4:1 to 9:1) in order to achieve high yields, while the solvent with more water leads to the formation of biphenyls.

3.3.5 Suzuki Coupling reactions using beads C and D

We adapted a method reported by Suzuki and co-workers for the coupling of phenylboronic acid with haloarenes in the presence of base to give biaryls in good yield.[140] It was found that the ideal conditions for the reaction utilised 3 mol% $Pd(PPh_3)_4$ as catalyst, with benzene or toluene as solvent (with toluene the reaction improved at high temperatures and for a longer reaction time) and two equivalents of aqueous sodium carbonate as base (relatively weak bases gave higher product yields).

It was decided to test beads **C** and **D** in several Suzuki coupling reactions to see whether the Suzuki coupling reaction works in the absence of a polar ethylene glycol film. For instance, the coupling of bromobenzene **51** with phenylboronic acid **114** using beads **C** or **D** as the catalyst, and sodium carbonate as the base in toluene, produced biphenyl **126** in good yield with low palladium leaching into the product as shown in the results table.



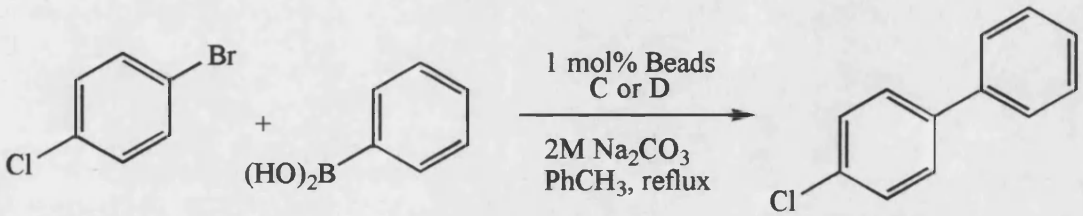
51 **114** **126**

Beads	Pd catalyst	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$PdCl_2$	5	85	<0.01 mg <0.1%
D	$PdCl_2$	5	87	<0.01 mg 0.1%
-	$PdCl_2$[a]	4	88	0.27 mg 10.3%

[a] triphenylphosphine ligand was also added.

The results compared the homogeneous system (which also used 1 mol% palladium chloride) with beads **C** and **D**. Both bead systems gave analogous results to the homogeneous in terms of yield and reaction time, but a substantial difference in palladium levels was noteworthy. The homogeneous system suffered from metal contamination in the biphenyl but the beads leached *only* 0.1% of the maximum amount of palladium that could have in theory leached into the product, which is an impressive result.

In another coupling reaction, 4-bromochlorobenzene **127** reacts with the boronic acid **114** to produce 4-chlorobiphenyl **128** in excellent yield with minimal palladium leaching using both beads **C** and **D**.



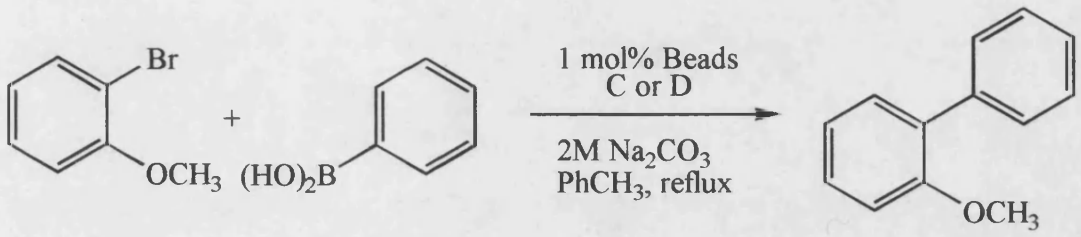
127 **114** **128**

Beads	Pd catalyst	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$PdCl_2$	4	84	<0.01 mg <0.1%
D	$PdCl_2$	4	86	<0.01 mg 0.1%
-	$PdCl_2$[a]	2	87	0.19 mg 7.1%

[a] triphenylphosphine ligand was also added.

The reaction times in all cases were rapid and palladium levels were extremely low in the bead system compared with the homogeneous counterpart.

Another Suzuki coupling is illustrated below that used identical conditions to couple 2-bromoanisole **129** with phenylboronic acid **114** to acquire the coupled product, 2-methoxybiphenyl **130** in exceptional yield.



129 **114** **130**

Beads	Pd catalyst	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
C	$PdCl_2$	8	74	<0.01 mg <0.1%
D	$PdCl_2$	7	95	<0.01 mg 0.2%
-	$PdCl_2$[a]	6	98	0.27 mg 10.4%

[a] triphenylphosphine ligand was also added.

Yet again, beads **C** and **D** gave good results and proved favourable over the homogeneous system.

Tests to show where palladium resides in a Suzuki coupling reaction

In order to try to establish how the reaction occurred with our bead system we carried out some test experiments to try to find out where the palladium lies during the Suzuki coupling reaction (i.e. which layer - organic or aqueous). For each test (❶-❺) the components (as indicated in **Table 4**) were introduced into a separatory funnel and toluene (10 ml) and water (10 ml) added.

The mixture was simply shaken in the separatory funnel, allowed to settle and the two layers extracted into separate flasks. To the organic layer, the solvent was removed *in vacuo*, aqua regia added and the sample diluted with distilled water. To the aqueous layer, aqua regia was added directly. Both samples were then analysed for palladium content (the dilution factor taken into account in each case). The different tests examined are shown in **Table 4** below with palladium content for each:

Table 4. Test for palladium during a Suzuki coupling reaction

Test	Davisil 500Å beads	Pd catalyst	Ligand(s)	Pd leaching (mg / %)	
				Organic	Aqueous
❶	✓	$PdCl_2$	TPPTS + TPP	0.04 mg 0.7%	5.24 mg 99.2%
❷	✓	$PdCl_2$	TPP	1.54 mg 29.2%	3.64 mg 69.0%
❸	✗	$PdCl_2$	TPPTS + TPP	1.44 mg 27.3%	3.77 mg 71.4%
❹	✓	$Pd(OAc)_2$	TPP	3.36 mg 63.9%	1.81 mg 34.4%
❺	✓	$Pd(OAc)_2$	TPPTS + TPP	2.36 mg 44.9%	2.84 mg 54.0%

For test ❶ which contains both TPP and TPPTS it is apparent that the palladium preferred to reside in the aqueous layer as palladium chloride is less organic soluble (palladium is detected in the aqueous solution). In this test an equal amount (in moles terms) of TPPTS and TPP were added and thus we can assume that the palladium had a greater affinity for the TPPTS than the TPP as only 0.7% of the total palladium added to the separatory funnel was actually found in the organic layer (a clear organic solution was observed). This theory was supported by the filter work carried out in **Chapter 4** where we performed a homogeneous reaction with TPP as ligand and after completion of the reaction, TPPTS was utilised as part of the filter system to remove any palladium.

In the absence of TPPTS (test ❷) most (69% of total palladium) remained attached to the beads (black coloured beads were monitored in the aqueous layer). These two tests also indicated that TPPTS was an essential component of the catalyst system to keep the palladium in the aqueous layer (as proved in section **2.5**). When TPPTS was absent more palladium was found in the organic layer (29.2%).

Results for test ❸ which contained similar components to test ❶ but beads were excluded from the former. Here we noted that by comparing the two tests we saw that more palladium entered into the organic layer and thus beads were also required in the catalyst to prevent palladium leaching into the organic layer (as shown in section **2.5**).

Tests ❹ and ❺ were performed to see where palladium acetate would lie rather than palladium chloride (tests ❶ to ❸) as used in earlier tests. Palladium acetate is organic soluble and hence we assumed it would prefer the hydrophobic environment. This suggestion was proved correct as palladium levels were higher in the organic layer (compared with tests ❶ and ❷ which only differed in type of palladium catalyst used). The water-soluble TPPTS did, however, retain more of the palladium in the aqueous layer.

Thus, it was thought that when performing a palladium catalysed reaction with any of the bead catalysts (with palladium acetate) it is requisite that the palladium must be complexed with the TPPTS (by heating) to ensure the catalyst is stable before performing a reaction, ensuing little or no palladium is leached into the organic layer.

In conclusion, all tests confirm that TPPTS and beads are essential components of the catalyst make-up and in the case with palladium acetate the palladium must be complexed (by heating) to the TPPTS before carrying out a reaction.

Conclusion

Both beads **C** and **D** have shown potential as catalysts in the Suzuki coupling reaction to give efficient results with little palladium leaching into the bulk organic layer. Beads **D** (with no ethylene glycol as a component of the complex) seemed more suitable for the task.

Surprisingly, the presence of aqueous sodium carbonate did not increase leaching significantly, although it is reasonable to assume that the beads have been hydrated.

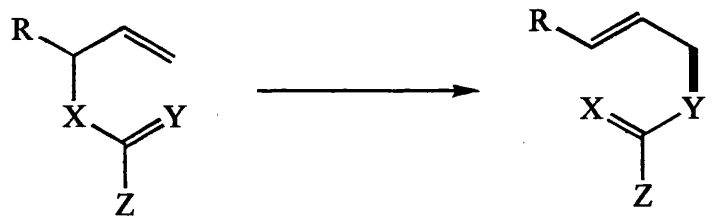
Further investigations into this matter have shown that the bead complex requires both TPPTS and beads for the palladium to remain within the aqueous layer.

3.4 Allylic rearrangement reactions

3.4.1 Introduction

The application of beads as catalysts in the [3,3]-sigmatropic rearrangement reactions aroused our curiosity as there is already a strong connection with this area within the group.[156] Much of the enzymatic work within the group focuses on combining an enzyme with a palladium catalyst to perform a dynamic kinetic resolution on certain allyl acetates using enzymatic hydrolysis to give the corresponding allyl alcohol. One method for *in situ* racemisation of the allyl acetate involves palladium (II) catalysis in order to obtain high enantioselectivities and high conversions. Palladium (II) catalysis was chosen since, in the mechanism, the acetate never leaves the substrate. However, for a palladium (0) catalysed racemisation, an intermediate allylpalladium complex can be attacked by nucleophiles other than acetate.

[3,3]-Sigmatropic rearrangements are important transformations in modern synthetic chemistry.[157] These reactions allow the allylic interchange of functionality X and Y **(131→132, Scheme 19)**, and often fashion the newly formed carbon-carbon double bond with a high level of stereocontrol.



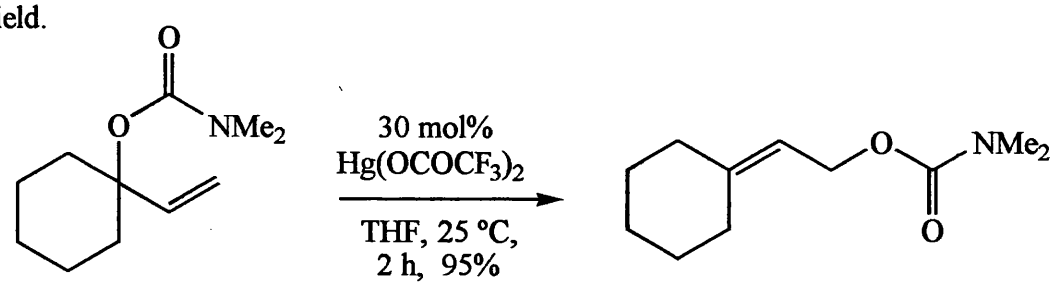
131 **132**

Scheme 19: The newly formed C-Y bond is sketched with a bold line.

It is not surprising that the development of catalytic methods for these important transformations has attracted widespread attention, and this area has been reviewed comprehensively by Lutz.[158] Perhaps the most versatile of the metal catalysts are the "soft" metal salts of Hg^{II} and Pd^{II}. These effectively catalyse a wide variety of [3,3]-sigmatropic rearrangements which form C-O, C-N, C-S, and C-C bonds (C-Y, **132**). Catalysed transformations of this type occur under extremely mild conditions (neutral pH and at, or near, room temperature) and often afford yields and regio- and stereoselectivities which far exceed those of their thermal counterparts.

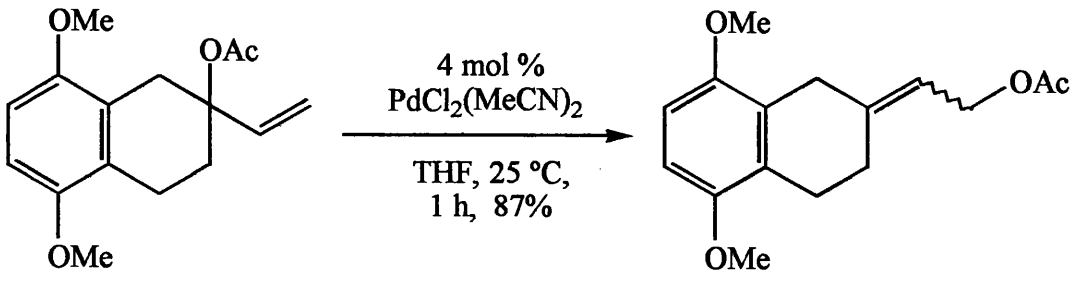
Allylic ester rearrangements

Catalysis of the equilibration of allylic esters by mercury (II) salts was first reported by Overman and Campbell in 1976.[159] Allylic carbamates equilibrated more readily than allylic anisoates or acetates, and anhydrous mercury (II) trifluoroacetate was found to be the catalyst of choice. One such example of application of this catalyst is given below where the carbamate **133** was treated with the mercury (II) trifluoroacetate in THF at room temperature to give the single rearranged carbamate product **134** in good yield.



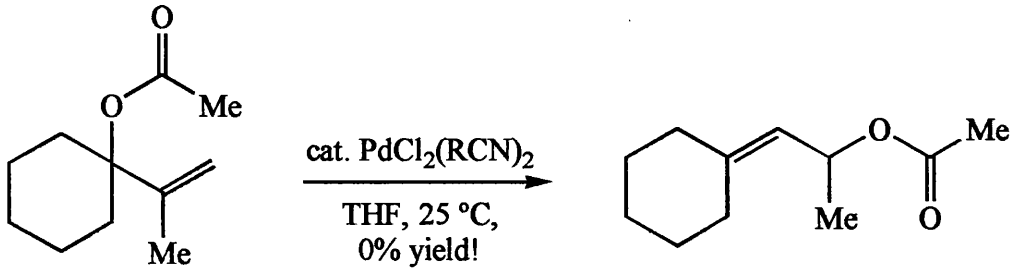
133 **134**

Palladium (II) salts were found to be even more effective than mercury (II) salts for equilibrating allylic esters.[160] For preparative purposes the most convenient method for equilibrating allylic esters was to use the palladium (II) chloride complexes of acetonitrile or benzonitrile in inert solvents such as THF, benzene, dichloromethane, or dichloroethene. This procedure was first described by Meyer,[161] and the method was further developed by Overman *et al*, who illustrated that a variety of allyl acetates could be equilibrated conveniently at room temperature in the presence of 1-8 mol% of $PdCl_2(MeCN)_2$.[160] For example, the conversion of **135** to **136** takes place cleanly to give a mixture of geometric isomers in high yield.



135 **136**

Like the mercury (II)-catalysed reaction, allylic ester rearrangements catalysed by palladium (II) chloride are limited to allyic esters which are unsubstituted at the C-2 position of the allyl group (e.g. **137** does not react to give **138**). Another exception would be substrates which contain ligands that coordinate strongly to palladium (II), such as dienes and alkynes.

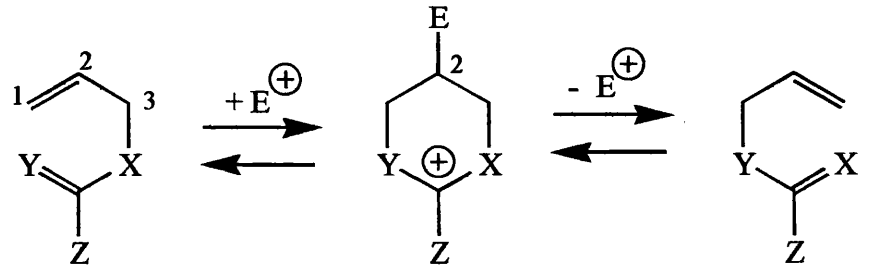


137 **138**

More recently, Overman *et al* demonstrated the use of an enantioselective palladium (II) complex containing chiral diamine ligands as an asymmetric catalyst for the rearrangement of allylic imidates to allyl amides[162] and the related rearrangement of allylic *N*-benzoylbenzimidates to allylic dibenzamides.[163]

3.4.2 Mechanism

Efforts to develop methods for catalysing [3,3]-sigmatropic rearrangements have been guided by the mechanistic paradigm Overman *et al* termed the *cyclisation-induced rearrangement catalysis* mechanism which may or may not be a proper mechanistic description of the palladium (II) catalysed reaction as depicted in **Scheme 20**. It is expected that soft electrophiles react with molecules such as **139** at a "soft" carbon-carbon π-bond, rather than a harder heteroatom, and thus promote polyene-like cyclisation to yield **140** (or a nucleophile-trapped equivalent). Fragmentation of **140** would afford the rearranged product **141**. For catalysis of this type to be effective, both the cyclisation and fragmentation steps have to be rapid, and the cyclic intermediate must be less stable than **139** and **141**.

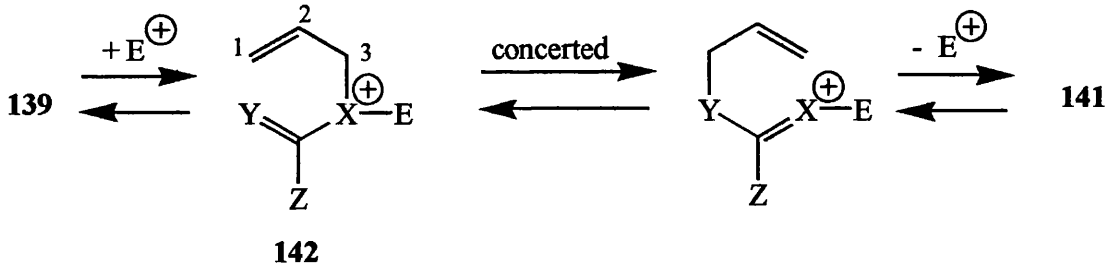


139 **140** **141**

Scheme 20

For mercury (II)- or palladium (II)-catalysed allylic ester rearrangements there is ample evidence to preclude mechanisms involving allyl cation or η^3-allylpalladium intermediates. In the various cases studied by Overman and co-workers catalytic transformations proceeded without scrambling of the allyl fragments (i.e. no competing [1,3]-shifts) and with clean suprafacial stereochemistry. In contrast, several related reactions which are catalysed by palladium (0) and probably involve η^3-allyl intermediates, do *not* show similar clean regio-[164] or stereochemical control.[165]

Mechanistically, a cyclisation-induced rearrangement (**Scheme 20**) or concerted charge-induced rearrangement (**Scheme 21**) would be consistent with these observations. Both mechanisms involve intramolecular re-organisation of a catalyst-substrate complex and thus would exhibit stereo- and regioselectivities similar to an intramolecular thermal rearrangement.



142

Scheme 21

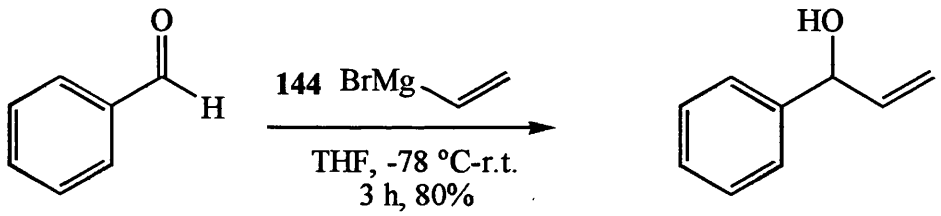
However, evidence accumulated to date is quite persuasive in favouring a cyclisation-induced rearrangement mechanism for allylic ester rearrangement reactions.

The major observations are: **(1)** soft electrophiles Hg (II) and Pd (II) are much more effective than hard Lewis or Brønsted acids in catalysing rearrangement of allylic imidates and allylic esters; **(2)** the general requirement that substrates **139** have a H atom at C-2 is consistent with the bonding of a bulky metal at this carbon. Alkyl substitution at this site should not dramatically decrease the rate of a concerted [3,3]-sigmatropic rearrangement of complex **142**; **(3)** intermediate **140** rationalises the rate of rearrangement in both mercury (II)-catalysed ($Z=NR_2>4$-methoxyphenyl$>CH_3$) and palladium (II)-catalysed ($Z=NR_2>OR>CH_3>CF_3$) reactions, since these relative rates directly parallel the stability of the carbocation **140**.

No literature work as known to date has been published on the use of solid supports or water-soluble ligands in the [3,3]-sigmatropic rearrangement of allylic esters using a palladium (II) catalyst. Hence, it inspired us to investigate this reaction using our bead system.

3.4.3 Allylic rearrangement reactions using beads C

Firstly, the substrates had to be synthesised before performing the rearrangement reaction. Hence, treatment of benzaldehyde **143** with a 1.0 M solution of vinyl magnesium bromide **144** in THF at -78 °C resulted in, after aqueous work-up and "flash" column chromatography, formation of the allylic alcohol **145** in good yield.

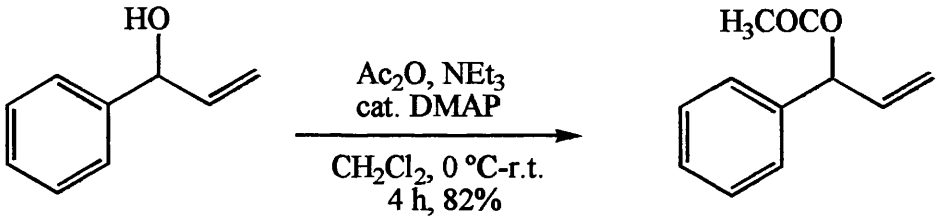


143 **145**

^{1}H NMR analysis of **145** confirmed product formation with the appearance of a one proton broad singlet at δ 2.4 ppm, corresponding to the proton of the hydroxy group.

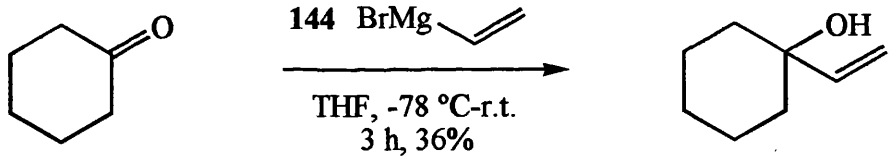
Acetylation of the allylic alcohol **145** was achieved using acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP in dichloromethane at room temperature.

^{1}H NMR analysis of **146** confirmed product formation with the disappearance of a one proton broad singlet at δ 2.4 ppm, corresponding to the hydroxy group of **145** and the appearance of a three proton singlet at δ 2.1 ppm, corresponding to the protons of the acetoxy group.



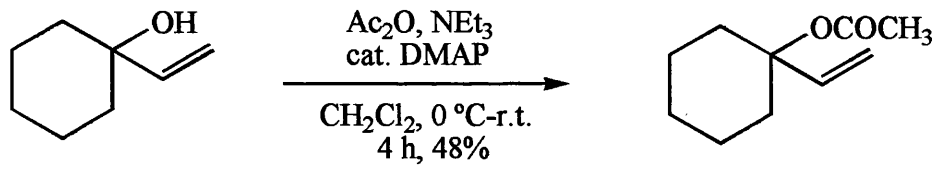
145 **146**

An alternative substrate for the allylic rearrangement reaction was synthesised by performing another Grignard reaction. Treatment of commercially available cyclohexanone **147** with 1.0 M vinyl magnesium bromide **144** in THF at -78 °C resulted in the formation of the corresponding allylic alcohol **148** in moderate yield. ^{1}H NMR analysis of **148** confirmed product formation with the appearance of a one proton broad singlet at δ 4.0 ppm, corresponding to the proton of the hydroxy group.



147 **148**

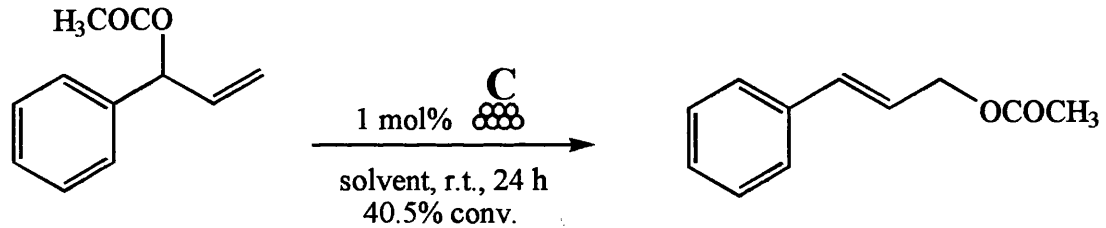
Acetylation of the allylic alcohol **148** was achieved using acetic anhydride, triethylamine as base in the presence of a catalytic amount of DMAP in dichloromethane at room temperature to give the ester **149** in reasonable yield. ^{1}H NMR analysis of **149** confirmed product formation with the disappearance of a one proton broad singlet at δ 4.0 ppm, corresponding to the hydroxy group of **148** and the appearance of a three proton singlet at δ 2.1 ppm, corresponding to the protons of the acetoxy group.



148 **149**

The substrates were then introduced into the palladium-catalysed allylic rearrangement reactions and hence the reactions were performed under mild conditions with low loadings of a palladium (II) catalyst. Thus, the conversion of the allylic acetate **146** in a suitable solvent to the rearranged product **150** was achieved using a palladium (II) catalyst at room temperature. **Table 5** shows the various reaction conditions attempted. The presence of product **150** was confirmed by ^1H NMR analysis. The analysis showed the disappearance of the one proton double double doublet at δ 6.1 ppm, corresponding to the *cis* vicinal coupling, and the appearance of a one proton double triplet at δ 6.2 ppm, corresponding to the *trans* vicinal coupling next to the methine group. It should be noted that the synthesis of the substrates for the allylic rearrangement reactions were not optimised for yield.

Allylic rearrangement reactions using beads



146 **150**

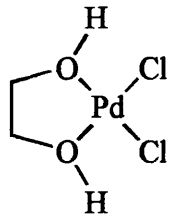
Initial work was performed on the homogeneous system to test the viability and set up conditions for GC analysis. For the homogeneous reaction, palladium (bisacetonitrile) dichloride was synthesised by simply stirring palladium chloride in refluxing acetonitrile. Once the homogeneous reaction was shown to give product, the product was analysed on the GC and conditions were optimised. The self-assembly beads (beads **C**) then came into operation. **Table 5** illustrates the results from the various reactions. Unfortunately, the conversions in the rearranged product proved less fruitful than those of the homogeneous counterpart.

The best conversion (with the beads) was obtained using THF as solvent but palladium leaching proved problematic as the polar solvent caused disintegration of the bead complex.

It was anticipated that the bead complex needed 'fine tuning' in attempt to improve the rearrangement reaction. We also tried using the palladium dichloride benzonitrile catalyst in the homogeneous system and found that the reaction was effective.

It was then decided to try and locate the problem and hence we compared the homogeneous system (which utilised the $PdCl_2(CH_3CN)_2$ ligand) with two other reactions which contained the same ingredients as the homogeneous system, but also the addition of an extra ligand. To one reaction TPPTS was added and the other contained TPP to see if the ligand was the culprit of poor yields in our bead systems. It was noted that conversions in the rearranged product were extremely poor compared with the reaction without addition of the TPPTS or TPP (as illustrated in **Table 5**) and hence we decided to pursue work with alternative ligands. Obviously the ligands used in the make-up of our bead complex caused drastic reduction in yield.

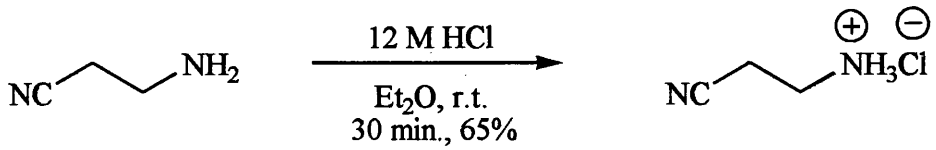
It was also felt that the ethylene glycol may have been acting as a bidentate ligand **151** and thus the palladium was unable to complex with the π bond in the alkene and perform the reaction, and it may also oxidise the palladium. The substrate did not appear to be very soluble in the non-polar solvent system employed in the reaction (i.e. hexane:ether, 2:1) so this could also be a further reason for poor reaction results.



151

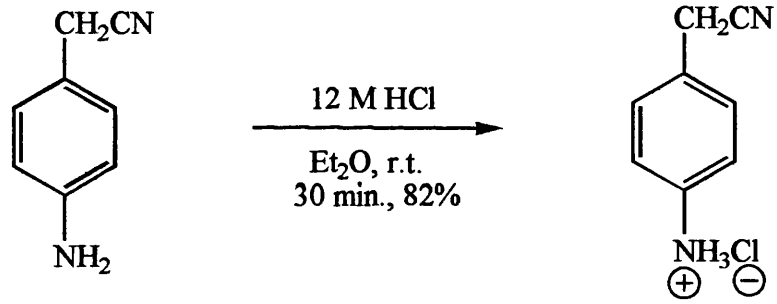
Thus it was envisaged that we could adapt the concept of using a similar catalyst system to the homogeneous system with a water-soluble nitrile ligand (similar to the two catalysts used in the homogeneous system i.e. acetonitrile and benzonitrile) variant as the ligand for our bead complex. Thus the following ligands were synthesised.

The first ligand was made by simple addition of acid to the 3-aminopropionitrile fumarate **152** to form the chloride salt **153** (referred to as ligand **A** in **Table 5**) which should have hydrophilic characteristics similar to the TPPTS ligand **8**.



152 **153**

The next ligand was formed by the same method as above by treating 4-aminobenzyl cyanide **154** with hydrochloric acid to form the chloride salt **155** (known as ligand **B** in **Table 5**).



154 **155**

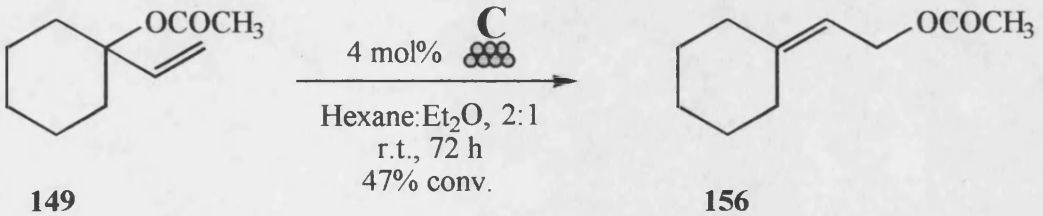
The final ligand, namely the sodium salt of cyanoacetic acid was kindly donated from a colleague and was labelled ligand **C** in **Table 5**.[166] As **Table 5** illustrates none of the ligands assisted the rearrangement reaction, in fact they appear to have hindered it. All rearrangement reactions in the table were measured after a 24 hour reaction time.

Table 5. The allylic rearrangement reaction to form **150**

Beads	Pd catalyst	Ligand[a]	Solvent	Yield (conv.)	Pd leaching (mg / %)
-	$PdCl_2(CH_3CN)_2$	-	THF	99.5[b]	HIGH[c]
-	$PdCl_2(CH_3CN)_2$	-	Hexane:Et_2O 2:1	NR	HIGH
-	$PdCl_2(PhCH_2CN)_2$	-	THF	98	HIGH
C	$PdCl_2$	TPPTS	THF	63	0.6 mg 9.50%
C	$PdCl_2$	TPPTS	Hexane:Et_2O 2:1	41	<0.01 mg 1.35%
-	$PdCl_2(CH_3CN)_2$	TPPTS	THF	4	-
-	$PdCl_2(CH_3CN)_2$	TPP	THF	0.8	-
C	$PdCl_2$	**A**	Hexane:Et_2O 2:1	NR	-
C	$PdCl_2$	**B**	Hexane:Et_2O 2:1	NR	-
C	$PdCl_2$	**C**	Hexane:Et_2O 2:1	NR	-

[a] ligands A,B and C were employed in allylic rearrangement reaction and are: **A** - Ammonium chloride salt of 3-aminopropionitrile fumarate, **B** - Ammonium chloride salt of 4-aminobenzyl cyanide and **C** - Sodium salt of cyanoacetic acid. [b]Corresponds with the literature (96 % after 8h). NR - no reaction. [c] "HIGH" values for palladium levels will be discussed further in Chapter 4.

The other allylic acetate **149** (again in a suitable solvent) was treated with a palladium (II) catalyst (beads **C**) at room temperature to give poor conversions of the allylic rearrangement product **156**. The presence of product **156** was confirmed by ^1H NMR analysis. The analysis indicated the disappearance of the *trans* and *cis* bonds, corresponding to **149** and the presence of one proton at δ 5.4 ppm corresponding to the double bond proton of the product **156**.



149 **156**

Beads	Pd catalyst	Ligand	Solvent	Reaction Time (h)	Yield (conv.)
-	$PdCl_2(CH_3CN)_2$	-	THF	2	93
-	$PdCl_2(PhCH_2CN)_2$	-	THF	3	98
C 	$PdCl_2$	TPPTS	Hexane:Et_2O 2:1	72	47

The results show the homogeneous system compared to the bead reactions. The bead reaction gave poor results and took a substantial amount of time for the product to form. The ligand TPPTS again seems to have a detrimental effect on the beads ability to catalyse the rearrangement reaction.[167]

N.B palladium levels were not measured as the bead reaction did not even compare to the homogeneous system in terms of yield or reaction time.

Conclusion

At this stage, we were having little success in applying bead **C** complex (i.e self-assembly style) to the allylic rearrangement reaction that it was decided to take an alternative approach to the problem. The presence of a phosphine ligand dramatically inhibited the reaction, presumably by blocking the co-ordination sites for the incoming alkene. We also tried making polar equivalents of the nitrile ligand which also proved inadequate. Other essential components of the bead complex were deemed unsuitable in the allylic rearrangement reaction, such as ethylene glycol which may act as a bidentate ligand and again block the pathway for alkene insertion. Thus, with little success in implementing the beads in such a reaction it was thought that we might be able to introduce the glass beads as a "sponge" after the homogeneous allylic ester rearrangement reaction had taken place to "mop-up" any palladium in the organic solution. This idea became more appealing and will be discussed in **Chapter 4**.

CHAPTER 4

THE USE OF GLASS BEADS AS SPONGES

4.1 Introduction

There is an increasing demand from environmental legislation, public and corporate pressure for a drive towards clean technology in industry. For many transition metal catalysed reactions, removal of the catalyst from the product presents difficulties, especially when reactions are performed on a large scale. Little work has been instigated in this area, despite the fact that the use of supported reagents as environmentally benign catalysts is well documented.[168] Much work has concentrated on producing new reagents which are environmentally friendly,[169] minimise waste and avoid use of toxic and/or hazardous reagents and solvents.[170,171] It is common knowledge that charcoal is a common reagent used in the removal of tetrakis(triphenylphosphine)palladium; however, a substantial amount is usually required.

Feng *et al* used mesoporous silica materials containing functionalised organic monolayers (of mercaptopropylsilane) to efficiently remove mercury and other heavy metals from both aqueous and non-aqueous waste streams.[172] Functional groups (thiol groups in this case) were introduced to the pore surface of mesoporous silica as the terminal groups of the monolayers. The hydrocarbon chains aggregated and formed close-packed arrays on the substrate. The siloxane groups then underwent hydrolysis and ultimately became covalently attached to the substrate and cross-linked to one another. Thus, one end group of the functionalised monolayers is covalently bonded to the silica surface and the other end group (containing the thiol group) can be used to bind heavy metals or other functional groups (**Figure 5**).

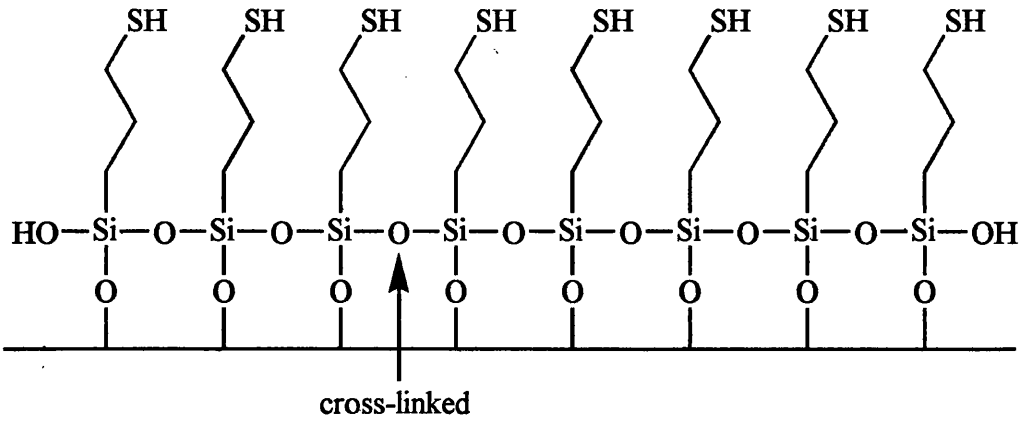


Figure 5

Treatment of the functionalised monolayers on mesoporous supports (FMMS) removed mercury from contaminated aqueous and organic solutions. A schematic (**Figure 6**) of the proposed structure with mercury bound to the thiol group is shown below. A single treatment with FMMS reduced the mercury concentration well below U.S Environmental Protection Agency elemental limits for hazardous wastes and even drinking water standards. More recently, an Austrian group reported use of dipyridyl amide-functionalised polymers for selective extraction of mercury and palladium.[173]

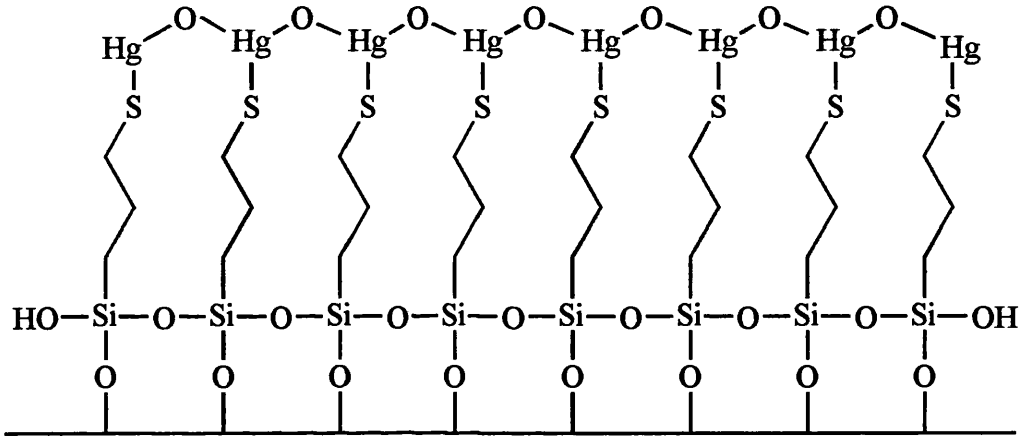


Figure 6

Degussa has synthesised a selective metal-absorbing resin called Deloxan® THP II which contains organofunctional polysiloxanes bearing thiourea, mercapto or thioether groups (e.g. **Figure 7**) to recover Rh, Pd, Pt, Ir, or Ru from *highly diluted* product or waste streams.[174]

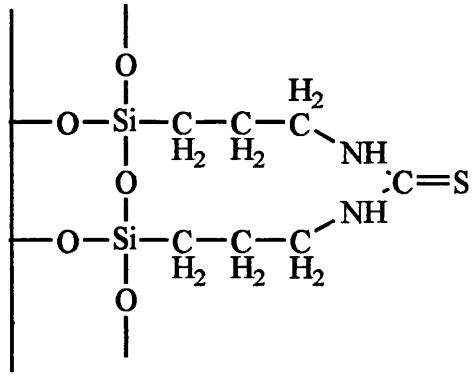


Figure 7

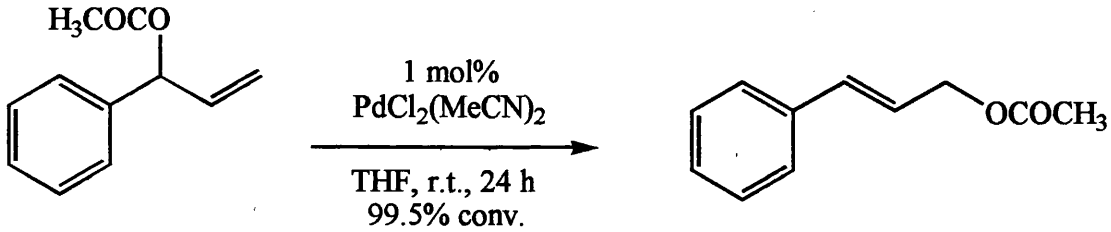
Few methods are given in the literature for the extraction of palladium. Nakashio *et al* selectively recovered palladium from a simulated industrial waste water by a liquid surfactant membrane (LSM) process.[175] They also used thiourea as a stripping agent to transport the palladium into the LSM system. Guy and Guyon synthesised six lipophilic thiacrown ethers for testing in the extraction of palladium (II) from nitric acid media and felt they may be able develop the technique and remove palladium from concentrated fission product solutions of nuclear fuel reprocessing.[176]

Our aim was to instigate a method for efficient extraction of palladium salts from organic media. Glass beads (Davisil) are able to support a hydrophilic film containing polar phosphine ligands. We wished to utilise this concept by demonstrating how these beads can act as 'sponges' to dramatically reduce levels of palladium in an organic solvent.

Our interest in removing palladium from a reaction arose from the disappointing results in the attempted development of a palladium (II)-catalysed rearrangement of allylic acetates using a supported catalyst (see section **3.4.3**).

4.2 Glass beads as palladium filters in the allylic rearrangement reaction

The rearrangement of allylic acetate **146** into the isomer **150** proceeds smoothly in the absence of a phosphine ligand (as discussed in section **3.4**).



146 **150**

However, as aforementioned, the use of a supported liquid phase catalyst does not appear to be possible using a polar phosphine ligand. Catalytic activity was found to be severely reduced in the presence of a phosphine (which competes with the alkene by co-ordinating to the palladium).

Hence we decided to use the standard homogeneous conditions and carry out the reaction five times using palladium bis(acetonitrile) dichloride as catalyst and then remove the palladium at the end of the reaction. When the reaction was complete, the product solution was decanted, the solvent removed *in vacuo* and palladium levels measured (Pd content of sample = 0.08 mg, **9.5%**).

To the other reactions the same procedures as just described were performed, but after removal of the solvent (THF), the product was re-dissolved in a less polar organic solvent (hexane:ether, 2:1). One equivalent of the pre-prepared (see **Table 6** for composition of each type of sponge bead) "sponge beads" (with respect to substrate) was added and the solution stirred for a few minutes ("stir-in" technique). The beads (various types of beads were employed as shown in **Table 6**) were decanted and the solvent removed *in vacuo* to yield a solid. The solid was tested for palladium content and the results were significant as the palladium level dropped to <0.1% of the total amount of palladium that could possibly leach, and visually the yellow solution rapidly became colourless. The beads became yellow instantly showing that palladium adhesion had occurred.

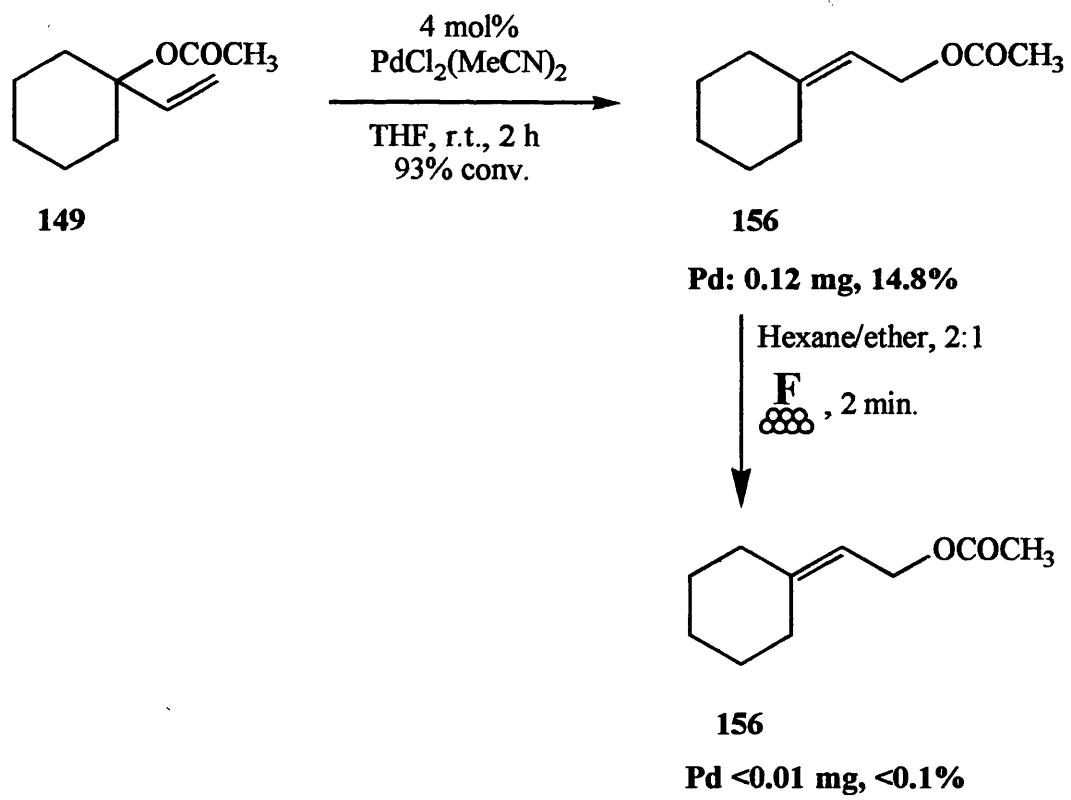
Table 6. Palladium extraction using different bead types

Beads (type)[a]	TPPTS	Ethylene Glycol	Pd leaching (mg / %)
CPG 239Å	✗	✗	<0.01 mg 0.7%
CPG 239Å	✓	✓	<0.01 mg <0.1%
Gly MPG	✗	✗	0.03 mg 4.2%
Gly MPG	✓	✓	<0.01 mg 0.6%

[a] Different types of beads were tested, namely CPG 239Å and Gly MPG (Glycerol coated beads).

From the table it is evident that the CPG (controlled pore glass) beads are superior to the glycerol coated beads (whether with or without ligand and ethylene glycol) to filter palladium. It is of paramount importance that TPPTS and ethylene glycol are components in the "sponge bead" synthesis.

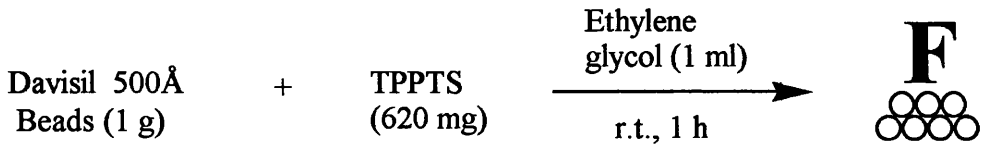
In another instance, the duplicate rearrangement of the acetate **149** into 1-cyclohexenyl acetate **156**, (see section **3.4**) the product in solution was decanted, solvent removed *in vacuo* and palladium content measured. To the other reaction, again the sample was re-dissolved in the less polar solvent and the solution stirred for a couple of minutes in the sponge beads (using the best preparation as shown in **Table 6** above). As depicted, a massive reduction in palladium was detected **(14.8% to <0.1%)**.



These results gave scope for further study in more widely used palladium-catalysed reactions and the optimum bead preparation had now been established.

4.3 Preparation of the sponge beads

Hence the sponge beads were synthesised simply by mixing the polar ligand (TPPTS) and Davisil beads (500Å)[177] in a minimal amount of ethylene glycol to form the palladium sponge as shown in **Scheme 22** below. The resulting glass bead sponge is a free-flowing powder which is easy to add to reaction mixtures, and subsequently filter.



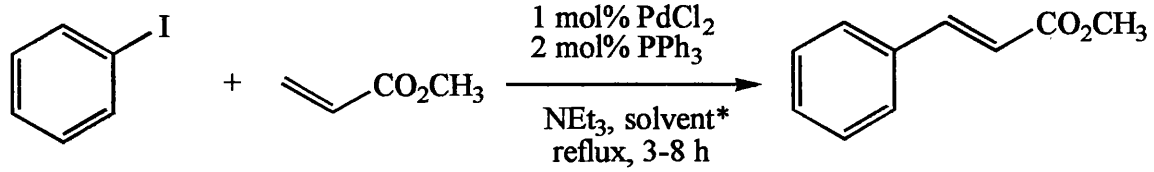
Scheme 22

The beads will be represented as  throughout the work.

4.4 Sponge beads in different palladium-catalysed reactions

Sponge beads used in the "filter" technique in the Heck reaction

The Heck coupling of iodobenzene **36** and methyl acrylate **49** affords cinnamate **50** in several solvent systems. The chemical yield for the reactions was 65-70%. The results are shown in **Table 7** illustrating the different types of filter that can be employed.



36 **49** 65-70% **50**

* solvents of varying polarity were screened to see how effective the sponge beads were.

The "filter technique" means simply taking the pre-prepared sponge beads () and introducing them to a bond elut tube. The sponge beads are compressed using a plunger to ensure maximum surface area in the bond elut for filter efficiency. The palladium contaminated sample is washed through the bond elut and the solution is collected in a test tube (see Diagram 1, Appendix for the set-up of the "filter technique").

The bond elut itself was measured as a control in **all** experiments studied and it was found that this alone reduced palladium levels substantially.[178]

Table 7. Comparison of decant and other filter methods with the "filter technique"

	Percentage of original palladium remaining[a]			
Isolation method	Dimethoxyethane	*iso*propyl alcohol	Acetonitrile	THF
Decant	7.2%	25.7%	30.6%	15.4%
Filter paper	5.9%	4.4%	10.0%	12.0%
10% beads[b]	0.6%	0.5%	0.1%	14.1%
50% beads[b]	0.2%	0.1%	0.1%	5.9%
100% beads[b]	0.2%	0.0%	0.0%	4.1%

[a] Palladium levels determined by ICP and the value is expressed as a percentage of the maximum theoretical amount which could be present.

[b] 10% beads corresponds to 10% w/w beads/substrate (P:Pd ratio 2.2:1).

The results summarised in **Table 7** indicate that by decanting off the solvent from the catalyst after the reaction, a high level of palladium is found, although the amount of palladium already precipitated depends on the solvent used. Palladium mirroring around the flasks was also observed.

Hallberg *et al* also found (after a reaction) a considerable amount of palladium covered the inside of the reaction vessel as a mirror.[95] Thus the metal had been transferred from the ligand attached to the glass, apparently *via* a soluble palladium intermediate. They postulated that the insertion of palladium into the aryl iodide occurred at the palladium metal surface and, after formation of a ligated arylpalladium iodide, coupling occurred. After reductive elimination, a part of the palladium employed was deposited as metal on the glass.

The results in the table show that filter paper removes some more of the palladium (refer to Diagram 2 in the Appendix for a difference in colour between decant and filter paper), but the palladium sponge gives extremely low levels of palladium in the final solution (<1% of original palladium remaining in all solvents except THF) *even* with low loadings of the Davisil glass beads.

It is important to note that the non-polar triphenylphosphine is competing with TPPTS for the palladium, and TPPTS must have a greater affinity for the palladium as the metal is adhering to the sponge beads. Perhaps, the triphenylphosphine is getting oxidised to triphenylphosphine oxide and hence it is no longer attached to palladium.

It is beneficial to note that the "filter technique" also provides an efficient metal filter for reactions carried out in acetonitrile. In section **2.5** it was evident that acetonitrile (i.e. polar solvents) could not be employed as solvent with any of our bead systems as it caused disintegration of the bead complex, yet it does not appear to destroy the sponge beads when filtering!

Conclusion

The "filter technique" provides an efficient way of removing palladium using *only* low loadings i.e. 10% w/w of the sponge beads. Hence, if only low amounts of the sponge beads are required for the filtration it is an economically viable process.

Sponge beads in the "stir-in" technique in the Heck and Suzuki coupling reactions

The same solvent tests were performed for the "stir-in" technique on the analogous Heck reaction as described in the "filter technique" (see above). Again a few examples of varying polarity solvents were selected and are shown in **Table 8** to give a flavour of the sheer capacity of the sponge beads () to extract palladium.

Table 8. Comparison of decant and other filter methods with the "stir-in technique"

	Percentage of original palladium remaining[a]			
Isolation method	Toluene	Butyl ether	Acetonitrile	THF
Decant	18.3%	3.3%	30.6%	15.4%
Filter paper	3.6%	0.4%	10.0%	12.0%
10% beads[b]	0.4%	0.0%	0.2%	15.8%
50% beads[b]	0.1%	0.0%	0.1%	10.2%
100% beads[b]	0.0%	0.0%	0.1%	3.9%

[a] Palladium levels determined by ICP and the value is expressed as a percentage of the maximum theoretical amount which could be present.

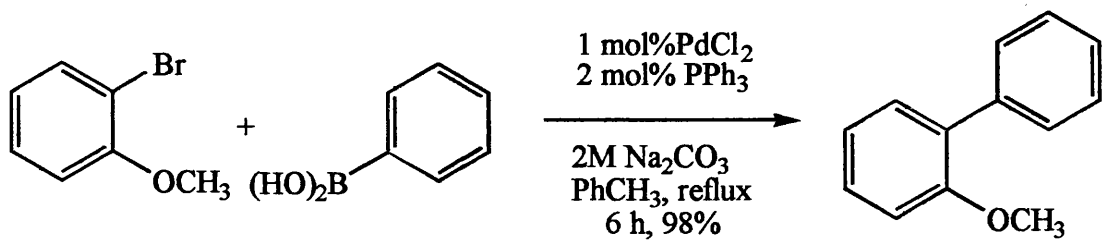
[b] 10% beads corresponds to 10% w/w beads/substrate (P:Pd ratio 2.2:1)

The "stir-in" technique simply involves introducing the pre-prepared sponge beads (beads **F**) directly into the reaction mixture and stirring the beads for a few minutes to allow the sponge to "mop up" any residual palladium. The beads are decanted from the reaction mixture and the solvent removed *in vacuo* to allow palladium determination.

Both the "filter technique" and the "stir-in technique" provide an efficient filter system for the removal of the transition metal in various types of solvents (except THF) even despite the presence of a non-polar ligand (triphenylphosphine), and required *only* low loadings (10% w/w) of sponge beads to carry out the task in hand (see Diagram 2, Appendix to illustrate the difference between decant, filter paper and sponge beads). The filter paper is inadequate compared to the "stir-in technique" as a filter. In most cases, extremely low levels of palladium were detected in the filtrate (≤0.4%). Interestingly, the palladium sponge can be used as a general reagent to extract palladium even from polar solvents such as acetonitrile.

Hence, with optimum conditions in hand we decided to use only 10% w/w sponge beads in other tests. Other examples of use of the "stir-in" technique have been applied to homogeneous palladium-catalysed reactions such as the Heck and Suzuki coupling reactions. However, one example was selected to illustrate the true potential of the sponge beads.

The coupling of 2-bromoanisole **129** with phenylboronic acid **114** using standard Suzuki coupling conditions (see section **3.3.5**) was carried out in duplicate, to give the biphenyl product **130** in good yield (98%).



129 **114** **130**

To one reaction, after separation of the layers, the toluene solution was decanted, solvent removed *in vacuo* and analysis of the palladium content was taken (palladium levels in filtrate 0.27 mg, **10.3%**). To the other reaction, after separation of the layers, 10% w/w of the sponge beads () were introduced to the flask and the beads were stirred for a few minutes. The beads were decanted from the solvent and the solvent removed *in vacuo*. Again, the palladium analysis was performed on the remaining solid (palladium levels in filtrate *only* 0.03 mg, **1.4%**). The "stir-in technique" reduced palladium levels to almost a tenth using *only* 10% w/w (with respect to substrate) sponge beads. Thus, the 'sponge' had to compete with any triphenylphosphine remaining in the organic solution for the palladium.

Conclusion

The "stir-in technique" also provides an effective filtration system for the extraction of palladium. Addition of a 'sponge' to a solution to remove palladium is an attractive, and useful approach, although it was felt that for some applications a filtration method may be more practical. With this in mind, we decided to pursue the work further.

Comparison of sponge beads with flash silica as palladium filters

For our purposes we chose to compare the sponge beads with flash silica as filters in the Heck reaction (see section **4.4**) with acetonitrile as solvent. Firstly, the "stir-in technique" was compared to flash silica as a palladium extractor, **100%** w/w flash silica was found to have a minimal affect on the level of palladium in the supernatant solution (26.5% of the original palladium present, compared to 30.6% for a simple decant, **Table 8**). By looking at **Table 8** using **10%** w/w sponge beads in the "stir-in technique", *only* 0.2% of the original palladium was present. Comparing the "filter technique" to flash silica (also contained within a bond elut) even at **100%** w/w a ten fold decrease was observed for the "filter technique" compared to flash silica as palladium filter.

In conclusion, flash silica does not compare with the sponge beads () used in either the "stir-in" or "filter" technique.

Conclusion of the different techniques for extracting palladium

Both the "stir-in" and "filter" techniques performed the task of eliminating palladium from the final product from Heck reactions in various solvent systems, except for THF which proved problematic. It is anticipated that a new type of filter needs to be synthesised for cleaning up palladium from *polar* solvents. One suggestion could be the synthesis of beads **E** (reverse phase supported catalyst) containing all but the palladium catalyst. This may be an idea for future development and implementation.

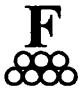
The "stir-in" technique is a good technique as it provides a large surface area of sponge beads in solution and palladium has a high contact time with the beads. However it is a "messy" technique as decantation is required to separate the beads from the organic solvent and this could prove problematic for large scale projects.

The "filter" technique uses the bond elut to contain the sponge beads. The bond elut itself removes some palladium so an authentic measure of the amount of palladium the actual sponge beads are removing cannot be assessed accurately. We also have the added complication of controlling the filtration rate. If we decide to apply pressure the flow rate of solvent through the bead bed will be quick and will not allow for the palladium to pass across the sponge beads effectively (i.e. a poor contact time).

However, if we use no pressure we obtain a good contact time and a slow flow rate (hopefully not too slow as time costs money!) which is ideal. This technique would be well suited for large scale synthesis as we could conceive that a cartridge could be loaded with the sponge beads and used directly in the scale up laboratory or pilot plant. Use of flash silica as a filter proved inadequate. One other advantage of the sponge beads is the possible use of the filter cake (containing the palladium) in a palladium-catalysed reaction (this is illustrated in section **4.7**).

Another idea that may work is to use a "teabag" or "dipstick" type filter. The "dipstick" idea may not be so effective though as some surface area of the sponge beads may be lost. We wished to broaden our horizons and find the optimum filter system which would remove *all* of the contaminating palladium from a solution and chose to focus our efforts towards designing a filter system for large scale applications.

4.5 Sponge beads used to extract palladium from a palladium solution

Preliminary investigations into the work included optimisation of ligand:palladium ratio to find the optimum sponge bead for maximum filter efficiency. Other factors had to be taken into account when designing a suitable carrier for the sponge beads () such as the type of carrier, length and diameter. The method of filtration also had to be considered such as whether to allow the palladium solution to filter through the sponge beads naturally ("gravity") or by applying pressure ("vacuum"). Each factor will be discussed in turn.

Type of filter method used - "gravity" and "vacuum"

As aforementioned, two methods of filtration were examined as discussed below:-

i) "Gravity" - for obvious reasons this method of filtration would be more efficient. The palladium solution would have a long contact time over the sponge beads and would utilise the large surface area coverage of the beads to its advantage. This method is suitable as long as the filtration is at a reasonable rate.

ii) "Vacuum" - this method uses low pressure to pull the palladium through and hence would not allow a long contact time for the palladium to pass over the sponge beads. However, the filtration would be quick.

Type of filter used and size

We utilised glass sinters to load our sponge beads for testing. This way we could either perform tests with or without assistance of pressure. Different diameter columns were investigated to optimise surface area for the palladium solution to pass over.

i) Exploratory results showed that a small diameter (0.5 cm) sinter funnel appeared to (have insufficient surface area) be too thin for the task as we could not employ the 'gravity" method of filtration as no palladium solution would go through. Thus we had to apply pressure by the "vacuum method" to manipulate the filtration and allow solvent to pass through. This method proved a poor filter system as it forced the palladium through and thus the filtrate contained a high palladium content.

ii) The larger diameter sinter (2 cm) also proved ineffective. Although this time we were able to use the "gravity" method and allow the solvent to flow through *very* slowly. The filter bed seemed too large for the amount of sponge beads and the column was loosely packed. Again some palladium passed through and high levels of palladium were found in the filtrate.

iii) The optimum sinter for filtration was the 1 cm diameter column as we could apply the "gravity" method to allow the palladium solution to pass over an efficiently packed bed of sponge beads () and ensure minimal amount of palladium passed through. Therefore, **Figure 8** portrays the type of filter set-up used in our experiments.

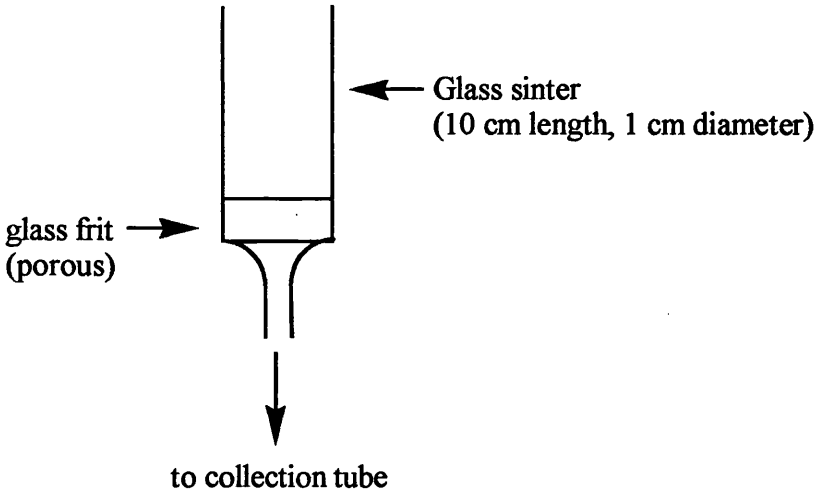


Figure 8

Optimisation of sponge bead preparation (i.e. TPPTS:Pd)

A solution of palladium acetate in toluene has been successfully filtered through a filter pad of the sponge beads (). The sponge beads were able to remove nearly all of the palladium from such solution in just one pass of the solution over the beads. Thus a solution of palladium acetate (50 mg) in toluene (10 ml) was passed over the glass bead sponges. The 10 ml solution was collected in 0.5 ml aliquots after filtration through the sinter, and the results are represented in Graph 1 in the Appendix. Three different quantities of sponge beads were tested to establish the ideal amount of sponge beads for application. Graph 1 depicts a Gaussian-shaped curve when using 1 g of the sponge beads (which contains 5 equivalents of TPPTS) which indicates that as the palladium solution goes through the sinter the sponge beads reach an equilibrium with palladium and the level of metal leaching is low. Eventually the sponge beads become less efficient as a filter (as no more palladium could be attached to the ligand, due to ligand saturation) and a little palladium leaches through. It should be noted that *only* 0.4% of the original palladium was present in the filtrate from all aliquots collected. Using 4 g of the sponge beads, the level was reduced to just **0.1%** of the original palladium present in the filtrate (Graph 1 shown as a dotted line, see key). Not surprisingly, even flash silica removed significant amounts of palladium when used in a filter (4.0 g affords 1.1% Pd in the filtrate), although this is over *ten* times less effective than using the glass bead sponges. Hence, if performing a multi-gram scale reaction 1.1% palladium may equate to more than the legal specification limit for palladium in the final product.

It was found that at higher ligand to palladium ratios less leaching was observed. However, a compromise between an acceptable level of palladium in the final solution and amount of ligand must be considered for economic reasons. Bearing in mind that in a typical palladium catalysed reaction the initial ratio of substrate to palladium can be 100:1 or higher, these filtration experiments provide a useful method for reducing palladium levels down to very low values in the final product. This methodology may have potential for use in extracting other metal contaminants after the metal catalysed reaction has gone to completion.

4.6 Future work

The aim would be to scale up the filter method now it has been optimised for large scale applicability, such as in the pilot plant of a pharmaceutical company. It would be envisaged that we could load a cartridge with our sponge beads and pass the product solution (contaminated with palladium) through the bed and measure the palladium levels of the filtrate (take a small sample and remove the solvent). If the palladium levels are too high, the sample would be dissolved in solvent and the sample passed through another cartridge until palladium levels are at a level acceptable for the required drug specifications (usually require <10 ppm Pd for pharmaceutical use).

For combinatorial chemistry the "stir-in" or "filter" technique would be suitable for multi-reactions. One alternative could be to place the sponge beads in a porous cap (with pores small enough so the beads do not leach out (i.e. < 500Å) but large enough to allow the palladium to attach to the beads), as displayed below in **Figure 9**.

We would simply take the reaction mixture (containing palladium) and add the sponge beads () to the cap (see **Figure 9, A**). The cap would be introduced to the solution and stirred for a few minutes (**B**). The cap would be removed to leave a palladium-free solution (**C**). The cap would have turned black due to the palladium.

This technique would be suitable for any palladium-catalysed reactions where the extraction of the metal is needed before continuing onto the next step in a synthesis. The cartridges could be cleaned and used time and time again so it would be cost effective.

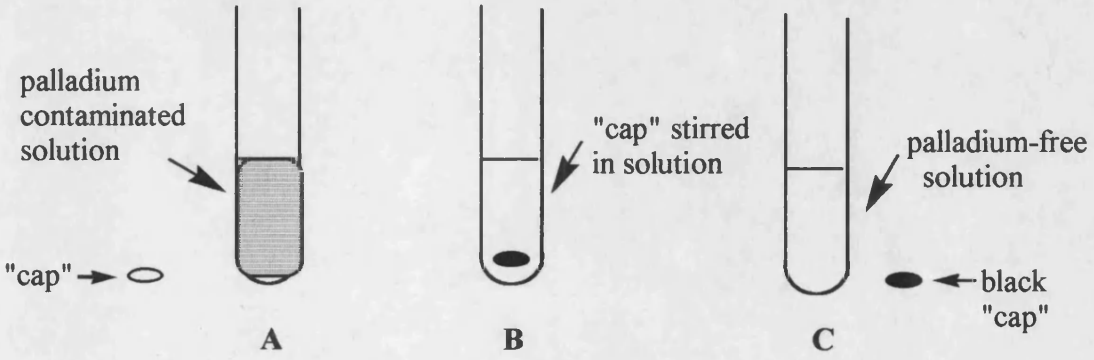


Figure 9

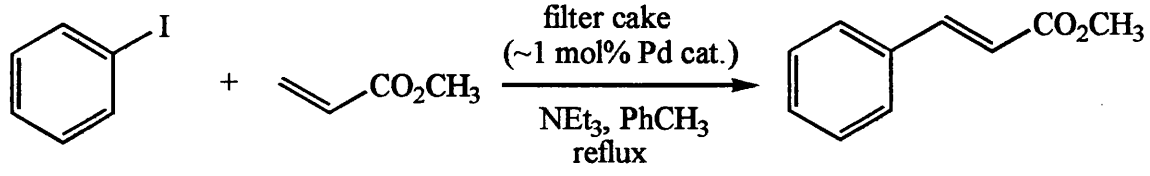
The ultimate objective would be to load a column with the bead catalyst (containing a high loading of palladium). A large flask would be prepared which contains all components of a Heck reaction (except for catalyst and ligand) and a small portion would be introduced to the column. At any one given time the loading of catalyst would be high and the reaction rate would be quick. After product is synthesised more substrate is introduced to the bead catalyst. This process continues and the product synthesised is passed through a bed of sponge beads () before being collected in a suitable vessel. This would ensure no palladium leaching into the product and allow for the continuous flow process which may reduce the level of TPPTS oxide produced. As the Heck cycle is continuous, there is less chance of oxidation to the TPPTS ligand. In the recycling experiments, (discussed in section **2.5**) after subsequent reactions some TPPTS may have been oxidised by air before performing the next experiment.

4.7 Miscellaneous tests

Use of a filter cake in a Heck reaction

We were fascinated to discover that the sponge beads could be isolated, and used as a catalyst for the Heck reaction to make methyl cinnamate. The Heck reaction was performed on a sample of filter cake from the filter tests carried out previously. The aim was to see if it was feasible to re-use the filter cake in a reaction or whether the palladium had been deactivated.

Hence the coupling between iodobenzene **36** and methyl acrylate **49** in toluene proceeded to yield the cinnamate **50** in good yield. In the first reaction the filter cake turned from black to green. The results found are illustrated below. The filter cake was recycled after the reaction, by degassing for one hour under a nitrogen atmosphere, and re-used again and this time the filter cake turned from green to black!.



36 **49** **50**

Reaction	Reaction Time (h)	Yield (%)	Pd leaching (mg / %)
1	5	74	<0.01 mg 0.1%
2	21	54	<0.01 mg <0.1%

Conclusion

The filter work is really remarkable as the sponge beads can be employed to absorb any residual palladium from the homogeneous reaction, and then the filter cake utilised as a catalyst to perform subsequent reactions with high activity and consistently low palladium leaching (0.1% after two consecutive reactions). Hence, two applications for the sponge beads () have been identified, one as a filter and the other as an active catalyst.

Can we perform a Heck reaction on beads and retrieve all the palladium?

The Heck reaction was performed on beads **C** (referred to in section **2.5**) to see whether all the palladium could be removed from the bead after the reaction, and thus the bead could be recycled. Hence the coupling of iodobenzene **36** to methyl acrylate **49** in toluene occurred after 4 hours to give the cinnamate **50**.

Various extraction methods took place to ensure all of the palladium was removed from the catalyst. Firstly, the reaction mixture was decanted from the beads, the solvent removed *in vacuo* and palladium measured in the bulk solvent (extraction **A**). Secondly, aqua regia (3 drops) was added to the beads, and the sample dissolved in distilled water, the beads were shaken and decanted from the aqueous layer to leave the beads. Again the aqueous layer was analysed for palladium leaching (extraction **B**).[179] Finally, a further amount of aqua regia (10 drops) was introduced to the beads and the bead mixture stirred for 24 hours. Distilled water was added to extract the palladium from the bead mixture and the aqueous layer decanted from the beads (extraction **C**). The table indicates that the total percentages for extractions **A** to **C** gave *almost* 100% palladium recovery. It is probable that the beads are clean and able to be recycled.

Extraction method	Pd leaching (%)
A	0.03
B	70.1
C	29.2

Conclusion

Glass bead sponges () prepared by coating glass beads with a film of ethylene glycol containing a polar phosphine ligand (TPPTS) were found to be highly effective for the removal of palladium from Heck product reaction mixtures, as well as from other palladium-containing solutions. Perhaps to illustrate the true potential of these beads as "sponges" to extract palladium, a large scale industrial application needs to be sought.

4.8 Summary and outlook

Glass bead technology has been applied successfully to many transition metal catalysed processes. The reactions retain much of the selectivity of their homogeneous counterparts, but keep the catalyst in a separate phase from the bulk reaction. Low levels of transition metal leaching are generally observed, which represents an economically sound and environmentally friendly approach to transition metal catalysed reactions.

Many palladium-catalysed reactions still need to be studied using glass bead technology, but the outlook is promising as the foundations have already been established.

CHAPTER 5

EXPERIMENTAL

5.1 General experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. "Light petroleum" refers to the fraction of petroleum ether boiling between 40 °C and 60 °C, and was distilled through a 36 cm Vigreux column over calcium chloride before use. Toluene was dried where necessary by storage over sodium wire for several days. Diethyl ether was distilled from sodium benzophenone ketyl under nitrogen, prior to use, as was tetrahydrofuran (THF). Dichloromethane was distilled from phosphorus pentoxide. Triethylamine was distilled from, and stored over potassium hydroxide. Davisil 300Å 653XWP (pore diameter, D_p = 300Å; surface area, SA =160 m^2/g) was purchased from Supelco Inc. and Davisil 500Å 663 XWP (D_p=500Å, SA=75-85 m^2/g) was purchased from Aldrich. Controlled pore glass beads (CPG Inc.), CPG-240B (D_p=239Å; SA=82 m^2/g), CPG-290B (D_p=290Å; SA=132 m^2/g), CPG-410B (D_p=410Å; SA=96 m^2/g) were obtained from Cambio Limited and donated by GlaxoWellcome. All porous silicas were vacuum dried overnight at 200 °C before use to remove residual moisture. Unless otherwise stated all starting materials used were obtained from commercially available sources.

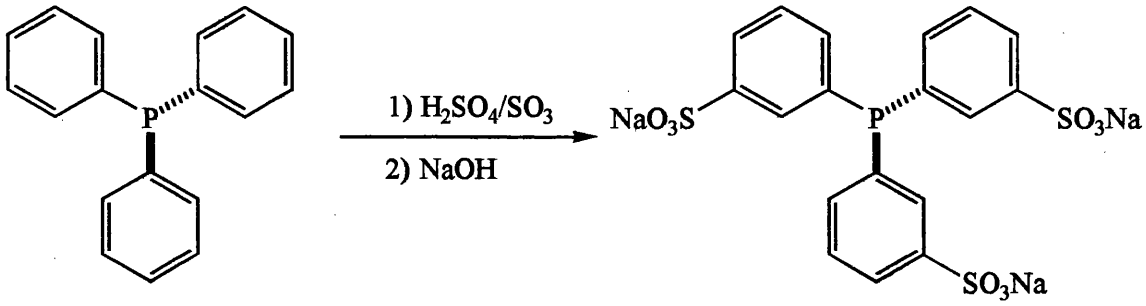
Analytical thin layer chromatography was carried out using precoated aluminium-backed silica plates (coated with Merck Kieselgel 60 GF_{254}). Plates were visualised under ultraviolet light (at 254 nm) or by staining with potassium permanganate solution or vanillin, followed by heating. "Flash" column chromatography was performed using Merck Kieselgel 60 H silica gel. Pressure was applied at the column head with hand bellows. Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent. Columns were collected and monitored by thin layer chromatography.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer and a Perkin-Elmer 1600 series FT-IR spectrophotometer, with internal calibration. Spectra were recorded as solutions in dichloromethane or as thin films. Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AC-250 and DPX 400 instrument and on the Jeol JNM-GX270 and EX-400. Chemical shifts were expressed in parts per million (ppm) downfield of tetramethylsilane (singlet at 0 ppm, TMS) for proton resonances and referenced to the central peak of the triplet of deuterated chloroform (77 ppm) for ^{13}C resonances. The multiplicities of the spectroscopic data are represented in the following manner; singlet (s), broad singlet (br s), doublet (d), double doublet (dd), broad doublet (br d), double triplet (dt), apparent triplet (app t), triplet (t), quartet (q) and multiplet (m). High and low resolution mass spectra were recorded on a Kratos MS80 instrument and the Micromass Autospec. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Gas chromatographic analysis was performed on a Pye Unicam instrument (column temp. 130 °C).

Atomic absorption analysis was carried out on a Perkin-Elmer 1100B spectrometer. Flame and graphite furnace techniques (sensitivity; 250 ppb with fuel lean flame and 10 ppb respectively) were employed using a HGA700 Graphite furnace and AS70 Autosampler and on the Varian AA-275 series AA spectrophotometer. The light source for Pd analysis was provided by a hollow cathode lamp from S+S Juniper Ltd. Palladium atomic absorption standard solution (1000 μg/ml in 5wt% HCl) was used and it was purchased from Aldrich Ltd. Samples for atomic absorption (AA) analysis were prepared in aqua regia/water mixture. For inductively coupled plasma (ICP) analysis the Varian liberty 200 instrument was used and all samples prepared in DMSO/ 2% HCl. A range of palladium standards were used for both atomic absorption and inductively coupled plasma experiments. Freeze-drying of the catalyst preparations was carried out on an Edwards Modulyo Pirani 10 Freeze Drier.

5.2 Experimental procedures for the preparation of different catalysts and ligand

Preparation of Trisulfonated triphenylphosphine (TPPTS)[108], 8.



Triphenylphosphine (10 g, 38.13 mmol) was added slowly to 100 ml of oleum (20% fuming sulfuric acid) at 0 °C. After allowing the reaction mixture to warm to r.t. the reaction was continued for 150 h to give complete sulfonation. The reaction mixture was then neutralised at 0 °C with 20% aqueous sodium hydroxide and the volume reduced to 200 ml. The residue was heated to reflux with 1000 ml of methanol and filtered hot. The solid was further extracted with 500 ml of hot methanol and the combined extracts were reduced to 200 ml in volume. Addition of 800 ml of acetone caused precipitation of the product (75-85% purity, the impurity being Na-TPPTS oxide). The sample was kept in the fridge overnight to allow further precipitation. Further purification was achieved by extraction with 300 ml of acetone/methanol/water, 10:5:1 followed by repeated dissolution (in 500 ml of hot methanol), re-precipitation (by adding 800 ml of acetone) and extraction (with 300 ml of acetone/methanol/water, 10:5:1) as illustrated above. After two repetitions of this purification procedure, the *title compound* **8** was produced as a colourless solid (11.90 g, 56%) with 97% purity as determined by ^{31}P NMR (161.98 MHz; D_2O) -4.30 ($P(C_6H_4SO_3Na)_3$.

Preparation of Beads A to F

Typical synthesis of Beads A

The catalyst consists of commercially available controlled pore glass (CPG), and prepared palladium catalyst, with sufficient ethylene glycol to coat the beads. A general procedure for the preparation of the catalyst is as follows:

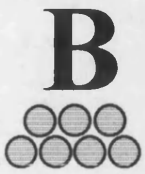
Synthesis of palladium complex

To a 50 ml round-bottomed flask was added palladium chloride (22.1 mg, 0.12 mmol, 1 mol%) and either monosulfonated triphenylphosphine **7** (100 mg, 0.27 mmol) ***or*** trisulfonated triphenylphosphine ligand **8** (156 mg, 0.27 mmol). Ethylene glycol (0.25 ml) was added into the reaction mixture to increase mixing between the two phases. The reaction mixture was stirred at 50-60 °C under a nitrogen atmosphere for 2 h. The red-brown colour gradually changed to a lime green colour as the palladium associated to the ligand. The palladium-ligand complex formed was a viscous green liquid.

Formation of Beads A

The CPG 290Å beads (250 mg) were impregnated with $PdCl_2(TPPMS)_2$ ***or*** $PdCl_2(TPPTS)_2$ (palladium-ligand complex) as the precursor in ethylene glycol (0.3 ml) to give a palladium loading of approx. 1 mol%. The reaction mixture was stirred for a further 30 min at r.t. under nitrogen to allow the beads to bind to the catalyst. After impregnation, the beads were washed with an excess of the reaction solvent to remove the part of the complex that was only physically absorbed. The beads were now ready for use in reactions and were stable and could be stored in a dessicator.

Typical synthesis of Beads B



A freeze-drying technique was employed in this series of experiments. The following general procedure was followed.

To a 50 ml round-bottomed flask was introduced palladium chloride (0.221 g, 1.25 mmol, 1 mol%) ***or*** palladium acetate (0.280 g, 1.25 mmol, 1 mol%) and trisulfonated triphenylphosphine ligand **8** (1.56 g, 2.74 mmol, 2.2 eq.). Ethylene glycol (5 ml) was added and the reaction mixture was heated to 50-60 °C under a nitrogen atmosphere for a period of 3 h to allow complexation to occur. The CPG 239Å beads (2.50 g) were weighed into the flask and a further 5 ml of ethylene glycol added. The flask was stirred at r.t. for 1 h to facilitate an even coating of the beads onto the catalyst complex. The prepared beads were initially cooled by freezing overnight then freeze-dried to remove all the ethylene glycol yielding a green solid. The solid was weighed and divided according to the amount required for the experiment (based on palladium catalyst).

For each weighing, beads **B** were reactivated by dosing with ethylene glycol (10 ml) lost on freeze-drying. The reaction solvent was added and the mixture was stirred at r.t. for 30 min. under a nitrogen pressure. The beads could now be used in various reactions.

Typical synthesis of Beads C

This synthesis is derived from a procedure reported by Davis *et al*[72a] which involves a self-assembly style bead preparation.

Derivatisation of the glass beads

To a 50 ml round-bottomed flask was added palladium chloride (22.1 mg, 0.12 mmol, 1 mol%) ***or*** palladium acetate (28 mg, 0.12 mmol, 1 mol%) and trisulfonated triphenylphosphine ligand **8** (TPPTS) (156 mg, 0.27 mmol) under a nitrogen atmosphere. Ethylene glycol (0.25 ml) was added into the reaction mixture to increase mixing between the two phases. The reaction solvent of choice was added and finally Davisil 500Å beads (250 mg) were added to the flask to allow complexation with the palladium complex.

For each palladium catalysed reaction

All the starting materials were then introduced into the flask and the reaction mixture was stirred at reflux under a nitrogen pressure until the reaction had gone to completion.

Typical synthesis of Beads D

Beads **D** were prepared without ethylene glycol. Hence the beads are a powder which can be synthesised in bulk and used directly in reactions.

To a 100 ml round-bottomed flask was added palladium chloride (88 mg, 0.50 mmol) ***or*** palladium acetate (111.3 mg, 0.50 mmol), trisulfonated triphenylphosphine **8** (620.8 mg, 1.09 mmol) and 40 ml methanol. The reaction mixture was stirred at 50-60 °C under a nitrogen atmosphere for 2 h. Davisil 500Å (1 g) was introduced and the mixture stirred at r.t. for a further 1 h. The reaction mixture was allowed to cool and the solvent was removed *in vacuo* to yield beads **D** as a powder which was dried overnight in an oven.

The $PdCl_2$ beads produced a lime green powder while the $Pd(OAc)_2$ beads gave a grey powder. The solid catalyst was weighed and divided according to the amount of palladium catalyst required for the reaction.

Typical synthesis of Beads E - *reverse phase catalyst*

Initially, the beads are derivatised with silane by adapting the Schott engineering method[110] before the catalyst and ligand is introduced.

Derivatisation of the glass beads

Into a 100 ml round-bottomed flask was added octyl trimethoxysilane (8.3 ml, 0.03 mol), Davisil 300Å (10 g) and absolute acetone (50 ml). The reaction mixture was stirred at 30 °C for 5 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to r.t. The reaction mixture was washed with 20 ml absolute acetone through a fire glass sinter under vacuum. The derivatised beads were dried in an oven overnight to yield a colourless powder.

i) Preparation of Beads E with tri-o-tolyl phosphine as ligand

To a 50 ml round bottomed flask was introduced palladium acetate (0.022 g, 0.10 mmol), tri-*o*-tolyl phosphine (0.122 g, 0.40 mmol, 4 mol% or 0.06 g, 0.20 mmol,

2 mol%), derivatised octyltrimethoxysilane Davisil 300Å beads (0.25 g) and cyclohexane (5 ml). The reaction mixture was stirred under a nitrogen atmosphere for 3 h at 65 °C. The reaction mixture was evaporated *in vacuo* to yield a fine yellow powder.

ii) Preparation of Beads E with TPP as ligand

To a 50 ml round-bottomed flask was introduced palladium acetate (0.022 g, 0.10 mmol), triphenylphosphine (0.066 g, 0.25 mmol, 2.5 mol%), derivatised octyltrimethoxysilane Davisil 300 Å beads (0.25 g) and cyclohexane (5 ml). The reaction mixture was stirred under a nitrogen atmosphere for 3 h at 65 °C. The reaction mixture was reduced *in vacuo* to yield a fine grey powder.

General work-up procedure when using any of the catalysts

After completion of the reactions using the various palladium catalysts the following procedure was adopted:

At the end of the reaction, the reaction mixture was separated from the catalyst by simple decantation or centrifuged for 1 min. to allow the catalyst to settle to the bottom of the tube and the organic solvent decanted off. The catalyst was washed three times with the reaction solvent and decanted repeatedly to ensure all free palladium was extracted and maximise product isolation. The organic solvent containing the reaction mixture was either:-

i) taken and reduced *in vacuo* to give the sample for palladium analysis, or
ii) submitted to the general work-up procedure to obtain a product yield.

Extraction of Palladium after reactions

General procedure

i) AA method

Filtered samples were evaporated at 400 °C and three drops of aqua regia were added to extract palladium. Deionised water (3 ml) was added and the samples were placed in an ultrasonicator to ensure all sample dissolved before carrying out the analysis.

ii) ICP method

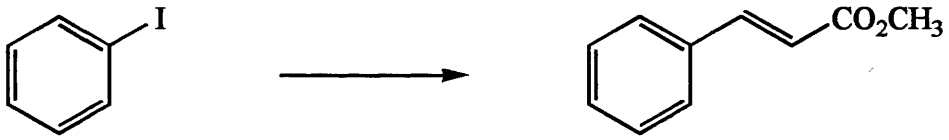
All samples were dissolved in 3 ml DMSO/2% HCl solution. The samples were placed in an ultrasonicator to ensure all sample dissolved before carrying out the analysis.

5.3 Chapter 2 experimental

Experimental procedures

Various Heck Reactions

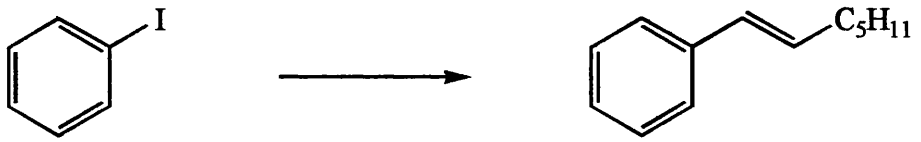
Typical synthesis of Methyl-*trans*-cinnamate, 50



In a typical vinylation experiment, Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)), toluene (5 ml), iodobenzene **36** (0.28 ml, 2.48 mmol), methyl acrylate **49** (0.28 ml, 3.10 mmol) and triethylamine (1.04 ml, 7.44 mmol) were introduced to a 50 ml round-bottomed flask equipped with a condenser. The reaction took place in a nitrogen atmosphere and the reaction mixture was heated under reflux until the reaction had gone to completion (3 h). The solvent was removed *in vacuo* and purified by "flash" column chromatography (eluant, light petroleum/ether, 3:1) to afford the *title compound* **50** as a pale yellow solid (0.286 g, 71%); Pd (<0.01 mg, 0.3%); mp 36-38 °C; bp 260-262 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 2930 (CH_3), 2885 (CH), and 1745 (CO_2CH_3); δ_H (250 MHz; $CDCl_3$) 7.68 (1 H, d, *J* 16.1, ArC<u>H</u>=CH), 7.49 (2 H, m,Ar<u>H</u>), 7.34 (3 H, m, Ar<u>H</u>), 6.42 (1 H, d, *J* 16.1, =C<u>H</u>CO_2CH_3), and 3.77 (3 H, s,

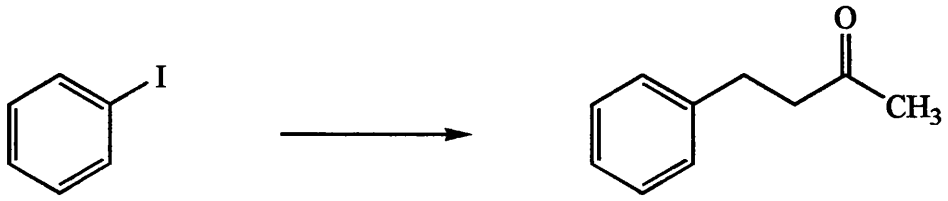
CH_3CO); δ_C (62.5 MHz; $CDCl_3$) 165.0 (CO), 141.3 ($CH=CHCO_2CH_3$), 134.9 (ArC), 128.4 (ArCH), 127.7 (ArCH), 126.2 (ArCH), 119.4 ($=CHCO_2CH_3$), and 50.5 (CH_3); *m/z* (EI) 162 (M^+, 85%), 131 (100), 103 (68), 91 (15), 77 (45), 51 (28), 43 (18), and 29 (14).

Typical synthesis of Phenyl-1-octene, 55



To a 50 ml round-bottomed flask was added Beads **B** (306 mg, $PdCl_2$ (0.12 mmol, 1 mol%)), hexane/ether, 4:1 (5 ml), iodobenzene **36** (1.39 ml, 12.46 mmol), 1-hexene **54** (1.86 ml, 14.96 mmol) and triethylamine (5.21 ml, 37.39 mmol). The reaction mixture was heated under reflux under a nitrogen atmosphere for 46 h. The solvent was removed *in vacuo* and purified by "flash" column chromatography (eluant, light petroleum/ether, 2:1) to afford the *title compound* **55** as an inseparable mixture (70% by ^1H NMR analysis). There is presence of product **55** in approx. 70%; δ_H (250 MHz; $CDCl_3$) 7.33 (X H, m, ArH), 6.40 (X H, d, *J* 15.8, $ArCH=CH(CH_2)_5$), 6.27 (X H, dt, *J* 15.8, 6.6, $ArCH=CH(CH_2)_5$), 2.15 (X H, m, $CH=CHCH_2(C_4H_9)$), 1.46 (X H, m, $CH_2(C_3H_6)CH_3$), and 0.91 (X H, t, CH_3). Other alkene protons were observed corresponding to other alkene regioisomers (total 30%), not assigned.

Typical synthesis of 4-Phenyl-2-butanone (Benzylacetone), 57



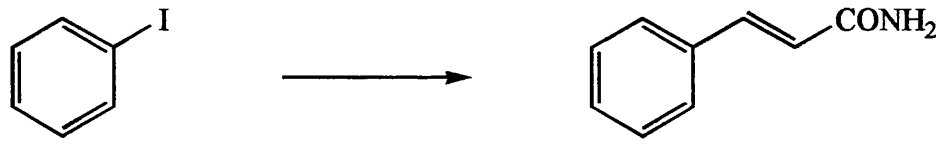
To a 50 ml round-bottomed flask was added Beads **B** (324 mg, $Pd(OAc)_2$ (0.12 mmol, 1 mol%)), hexane/ether, 4:1 (5 ml), iodobenzene **36** (1.39 ml, 12.46 mmol), 3-buten-2-ol **56** (1.35 ml, 15.60 mmol) and triethylamine (2.17 ml, 15.60

mmol). The reaction mixture was heated under reflux with a nitrogen pressure for 48 h. The reaction mixture was allowed to cool, treated with water (25 ml) and extracted into ether (3 x 25 ml), and the ether layer was separated. After the ether phase was concentrated the *title compound* **57** was obtained as a colourless oil (1.630 g, 88%); Pd (<0.01 mg, <0.1%); bp 234 °C (27 mm Hg); ν_{max} ($CHCl_3$)/cm^{-1} 2930.0 (CH), and 1715.0 (CO); δ_H (250 MHz; $CDCl_3$) 7.2 (5 H, m, ArH), 2.75 (4 H, m, CH_2CH_2), and 2.1 (3 H, s, CH_3); δ_C (62.5 MHz; $CDCl_3$) 207.1 (CO), 137.3 (ArC), 128.3 (ArCH), 126.4 (ArCH), 125.7 (ArCH), 45.0 (CH_2CO), 41.0 (CH_2CH_2), and 24.0 (CH_3); *m/z* (EI) 148 (M^+, 34%), 105 (52), 91 (48), 87 (100), 77 (17), 65 (9), 51 (13), 43 (88), 39 (12), and 27 (11).

Typical synthesis of 1-Bromo-2-methyl-*trans*-cinnamate, 62

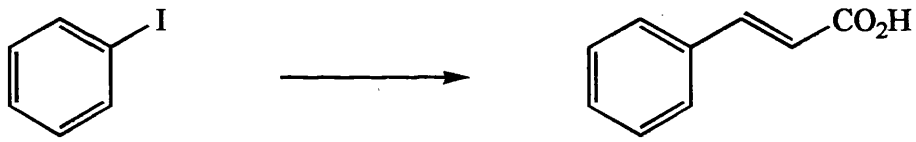
To a 50 ml round-bottomed flask was added Beads **B** (324 mg, $Pd(OAc)_2$ (0.12 mmol, 1 mol%)), hexane/ether, 4:1 (5 ml), 1-iodo-2-bromobenzene **61** (1.60 ml, 12.46 mmol), methyl acrylate **49** (1.40 ml, 15.60 mmol) and triethylamine (3.47 ml, 24.92 mmol). The reaction mixture was heated under reflux under a nitrogen atmosphere for 47 h. The solvent was removed *in vacuo* and purified by "flash" column chromatography (eluant, light petroleum/ether, 2:1) to produce the *title compound* **62** as a colourless solid (1.781 g, 59%); Pd (<0.01 mg, <0.1%); ν_{max} (CH_2Cl_2)/cm^{-1} 2930 (CH_3), 2885 (CH), 1745 (CO_2CH_3); δ_H (250 MHz; $CDCl_3$) 8.00 (1 H, d, *J* 16.2, ArCH=CH), 7.70 (2 H, m, ArH), 7.45 (3 H, m, ArH), 6.80 (1 H, d, *J* 16.2, ArCH=CH), and 3.75 (3 H, s, CH_3); δ_C (62.5 MHz; $CDCl_3$) 166.0 (CO), 143.0 ($CH=CHCO_2CH_3$), 142.7 (ArC), 134.2 (ArCH), 131.3 (ArCH), 127.4 (ArCH), 126.2 (ArCH), 121.2 (ArCBr), 120.4 ($=CHCO_2CH_3$) and 52.1 (CH_3); *m/z* (EI) 242/240 (M^+, 15/14), 209/207 (18/19), 161 (100), 118 (35), 102 (68), 75(30), 51 (26), and 29 (10).

Typical synthesis of Cinnamamide, 64



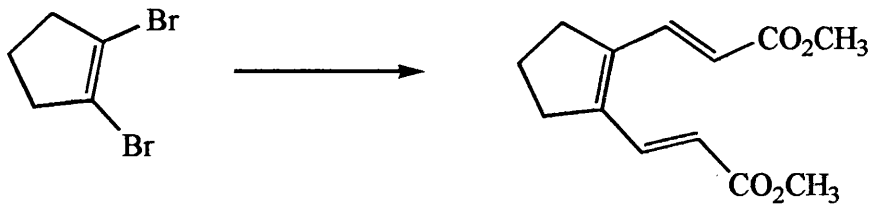
To a 50 ml round-bottomed flask was added Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)), toluene (5 ml), iodobenzene **36** (0.28 ml, 2.48 mmol), acrylamide **63** (0.22 g, 3.10 mmol) and triethylamine (1.04 ml, 7.44 mmol). The reaction took place in a nitrogen atmosphere and the reaction mixture was heated under reflux for 23 h. The solvent was removed *in vacuo* to yield the *title compound* **64** as a colourless solid (0.238 g, 65%); Pd (<0.01 mg, 0.2%); mp 148-149 °C (lit.,[180] mp 148-150 °C); δ_H (250 MHz; $CDCl_3$) 7.55-7.33 (5 H, m, ArH), 7.56 (1 H, d, *J* 15.9, =CH), 7.10 (2 H, br s, $CONH_2$), and 6.72 (1 H, d, *J* 15.9, CH=).

Typical synthesis of Cinnamic acid, 65



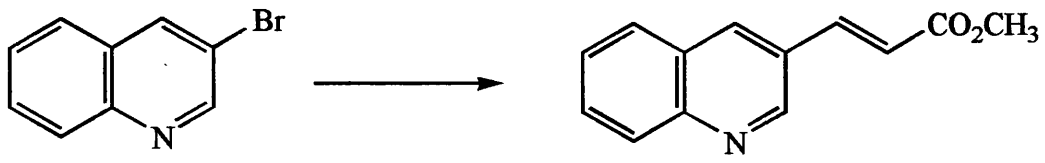
To a 50 ml round-bottomed flask was added Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)), toluene (5 ml), iodobenzene **36** (0.28 ml, 2.48 mmol), acrylic acid **41** (0.21 ml, 3.10 mmol) and triethylamine (1.04 ml, 7.44 mmol). The reaction took place in a nitrogen atmosphere and the reaction mixture was heated under reflux until the reaction had gone to completion (25 h). The solvent was removed *in vacuo* to give the *title compound* **65** as a colourless solid (0.244 g, 66%); Pd (<0.01 mg, 0.3%); mp 130-132 °C (lit.,[180] mp 133-134 °C); δ_H (250 MHz; $CDCl_3$) 12.67 (1 H, br s, CO_2H), 7.83 (2 H, m, ArH x 2), 7.63 (1 H, d, *J* 15.8, =CH), 7.44 (1 H, t, *J* 7.7, ArH), 7.16 (1 H, dt, *J* 7.7, 1.5, ArH), and 6.42 (1 H, d, *J* 15.8, CH=).

Typical synthesis of Methyl 3-(*E*)-{2-[2-(*E*)-methoxycarbonylethenyl]cyclopent-1-enyl}acrylate, 72



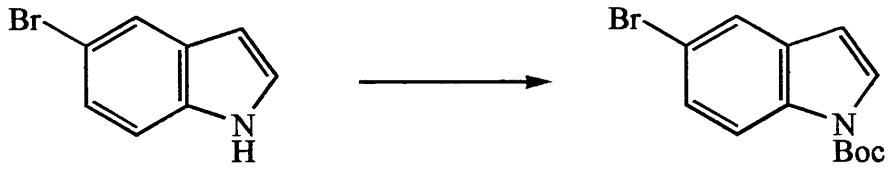
A mixture consisting of 1,2-dibromocyclopentene **69** (0.12 ml, 1 mmol), methyl acrylate **49** (0.45 ml, 5 mmol), triethylamine (0.50 ml, 4 mmol) and toluene (5 ml) were placed in a thick-walled pyrex bottle equipped with magnetic stirrer. The solution was purged with nitrogen, then Beads **C** ($Pd(OAc)_2$ (23 mg, 0.1 mmol, 10 mol%)) were added. After heating with stirring under reflux for 27 h and the mixture was then cooled to r.t. The reaction mixture was added to dichloromethane (50 ml) and washed with water (5 x 25 ml). The aqueous layer was extracted twice with dichloromethane and the organic layers dried with magnesium sulfate. The solvent was evaporated *in vacuo* and the residue purified by "flash" column chromatography (eluant, light petroleum/ether, 4:1) to give the *title compound* **72** as a colourless crystalline solid (0.165 g, 69%); Pd (<0.01 mg, <0.1%); mp 90-92 °C; (Found: C, 64.6; H, 6.8; N, 0.3 containing approx. 5% triethylamine. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); (Found: M^+, 236.1057. $C_{13}H_{16}O$ requires 236.1049); ν_{max} (CH_2Cl_2)/cm^{-1} 2952, 2942, 2845 (OCH_3), 1719 (CO_2CH_3), 1435, 1273, 1167 (CO), 974 (C=C), and 856; δ_H (250 MHz; $CDCl_3$) 7.86 (2 H, d, *J* 15.5, C<u>H</u>=CHCO$_2$CH$_3$), 5.93 (2 H, d, *J* 15.5, =C<u>H</u>CO$_2$CH$_3$), 3.79 (6 H, s, C<u>H</u>$_3$), 2.67 (4 H, t, *J* 7.9, C=CC<u>H</u>$_2$), and 1.95 (2 H, quintet, *J* 7.9, C<u>H</u>$_2$); δ_C (100.4 MHz; $CDCl_3$) 167.4 (<u>C</u>O), 144.3 (<u>C</u>), 136.0 (<u>C</u>H=CHCO$_2$CH$_3$), 120.8 (=<u>C</u>HCO$_2$CH$_3$), 51.7 (<u>C</u>H$_3$), 33.6 (C=<u>C</u>CH$_2$), and 21.3 (<u>C</u>H$_2$); *m/z* (EI) 236 (M^+, 22%), 204 (36), 177 (48), 161 (7), 145 (53), 131 (7), 117 (89), 98 (18), 91 (41), 84 (100), 77 (18), 66 (5), and 59 (29).

Typical synthesis of (*E*)-Methyl 3-(3-quinolyl)acrylate, 74



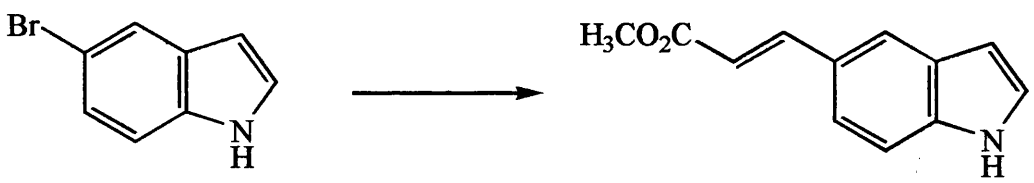
A solution of 3-bromoquinoline **73** (0.14 ml, 1 mmol), methyl acrylate **49** (0.11 ml, 1.25 mmol), Beads **Ei** (375 mg, $Pd(OAc)_2$ (0.01 mmol, 1 mol%), ligand (0.04 mmol)) and triethylamine (0.42 ml, 3 mmol) was heated under nitrogen in a heavy-walled pyrex tube under reflux until TLC (light petroleum/ethyl acetate, 1:3) showed reaction had gone to completion (14 h). The reaction mixture was cooled and separated with water (25 ml) and dichloromethane (50 ml). After washing with water (3 x 25 ml) the organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was recrystallised from chloroform to give the *title compound* **74** as a pale yellow crystalline solid (0.178 g, 83%); Pd (<0.01 mg, <0.1%); mp 117-119 °C; (Found: C, 73.2; H, 5.2; N, 6.5. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%); (Found: M^+, 213.0784. $C_{13}H_{11}NO_2$ requires 213.0790); ν_{max} (CH_2Cl_2)/cm^{-1} 1713 (CO), 1633 (C=N), 1432, 1263/1171 (CO), and 981 (CH=CH *trans*); δ_H (250 MHz; $CDCl_3$) 9.02 (1 H, d, $J_{H2,H4}$ 2.0, H_2), 8.18 (1 H, d, $J_{H2,H4}$ 2.2, H_4), 8.06 (1 H, d, $J_{H7,H8}$ 8.2, H_8), 7.81-7.66 (3 H, m containing (1 H, d, J 16.1, C<u>H</u>=CHCO$_2$CH$_3$) and (1 H, $J_{H7,H8}$ 8.4, $J_{H6,H7}$ 5.5, $J_{H5,H7}$ 1.5, H_7), (1 H, $J_{H5,H6}$ 8.4, $J_{H5,H7}$ 1.5, H_5), 7.53 (1 H, $J_{H5,H6}$ 8.1, $J_{H6,H7}$ 5.9, $J_{H6,H8}$ 1.1, H_6), 6.61 (1 H, d, J 16.1, =C<u>H</u>CO$_2$CH$_3$), and 3.78 (3 H, s, C<u>H</u>$_3$); δ_C (100.4 MHz; $CDCl_3$) 166.4 (<u>C</u>O), 148.8 (C2), 148.1 (<u>C</u>N), 141.0 (<u>C</u>H=CHCO$_2$CH$_3$), 135.0 (C4), 130.2 (C7), 129.0 (C8), 128.0 (C5), 127.0 (C6 and <u>C</u> x 2), 119.3 (CH=<u>C</u>HCO$_2$CH$_3$), and 51.5 (<u>C</u>H$_3$); *m/z* (EI) 213 (M^+, 66%), 198 (20), 182 (100), 170 (17), 154 (42), 127 (35), 101 (15), 91 (7), 77 (26), 63 (13), 51 (17), and 43 (33).

N-tert-Butoxycarbonyl-5-bromoindole, 76[181]



To a solution of 5-bromoindole **75** (392 mg, 2 mmol) and DMAP (20 mg) in dichloromethane (10 ml), di-*tert*-butyl dicarbonate (654 mg, 3 mmol) was added. The mixture in the two-necked flask was stirred for 1 h under a nitrogen pressure at r.t. The reaction was monitored by TLC (light petroleum/ethyl acetate, 5:1). After completion *N,N*-dimethyl ethanolamine (0.5 ml) was added and the mixture stirred for a further 15 min. The colourless solution was transferred into a separation funnel, diluted with ether (50 ml) and washed with 2 M nitric acid (3 x 25 ml) and concentrated $NaHCO_3$ solution (2 x 25 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was dissolved in ether (10 ml) passed through a short silica column (0.5 x 3 cm) and concentrated again to give yellow crystals (590 mg, 99%); δ_H (250 MHz; $CDCl_3$) 8.02 (1 H, d, $J_{H6,H7}$ 8.8, H_7), 7.69 (1 H, d, $J_{H4,H6}$ 1.8, H_4), 7.58 (1 H, d, J 4.1, H_2), 7.39 (1 H, dd, $J_{H6,H7}$ 8.8, $J_{H4,H6}$ 1.8, H_6), 6.50 (1 H, d, J 4.1, H_3), and 1.67 (9 H, s, CH_3 x 3); δ_C (67.80 MHz; $CDCl_3$) 132.7 (CN), 132.2 (C), 127.0 (C2 and C5), 123.5 (C6), 116.5 (C4), 115.9 (C7), 106.4 (C3), 84.1 (CCH_3), and 28.1 (CH_3 x 3).

Typical synthesis of (*E*)-Methyl 3-(5-indolyl)acrylate, 78

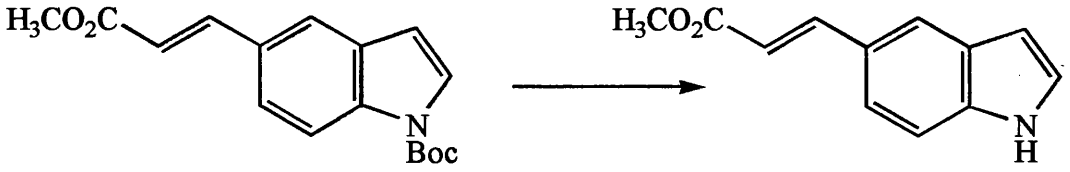


5-bromoindole **75** (0.20g, 1 mmol), methyl acrylate **49** (0.11 ml, 1.25 mmol), triethylamine (0.42 ml, 3 mmol), Beads **Ei** (318 mg, $Pd(OAc)_2$ (0.01 mmol, 1 mol%), ligand (0.02 mmol)) were heated in a thick-walled pyrex tube with a nitrogen pressure under reflux for 15 h. The reaction mixture was cooled and was diluted with water

(25 ml) and dichloromethane (50 ml). After washing with water (3 x 25 ml) the organic layer was dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue purified by "flash" column chromatography (eluant, light petroleum/ethyl acetate, 3:1) to give the *title compound* **78** as a colourless crystalline solid (0.105 g, 52%); Pd (<0.01 mg, <0.1%); mp 140.0-142.0 °C (lit., [182] mp 141.0-142.0 °C); (lit[131] found: C, 71.4; H, 5.4; N, 6.9. $C_{12}H_{11}NO_2$ requires C, 71.6, H, 5.5; N, 7.0%); (Found: M^+, 201.0782. $C_{12}H_{11}NO_2$ requires 201.0790); ν_{max} (CH_2Cl_2)/cm^{-1} 3321 (NH), 1694 (CO), 1284/1224/1184 (CO), 855, 803, and 766; δ_H (250 MHz; $CDCl_3$) 8.36 (1 H, br s, NH), 7.85 (1 H, d, *J* 15.9, CH=CHCO$_2$CH$_3$), 7.80 (1 H, br s, H_4), 7.41 (2 H, m, contains (1 H, $J_{H6,H7}$ 8.4, H_7), (1 H, $J_{H6,H7}$ 8.6, H_6), 7.24 (1 H, app t, $J_{H2,H3}$ 2.6, H_2), 6.59 (1 H, t, $J_{H2,H3}$ 2.6, H_3), 6.42 (1 H, d, *J* 15.9, CH=CHCO$_2$CH$_3$), and 3.81 (3 H, s, CH$_3$); δ_C (100.4 MHz; $CDCl_3$) 168.1 (CO), 146.7 (CH=CHCO$_2$CH$_3$), 137.0 (CN), 128.1 (C5), 126.5 (C), 125.3 (C2), 122.4 (C4), 121.6 (C6), 114.6 (=CHCO$_2$CH$_3$), 111.6 (C7), 103.4 (C3) and 51.5 (CH$_3$); *m/z* (EI) 201 (M^+, 100%), 195 (7), 170 (80), 142 (25), 115 (27), 89 (9), 85 (6), 71 (22), 63 (8), 58 (5), and 43 (22).

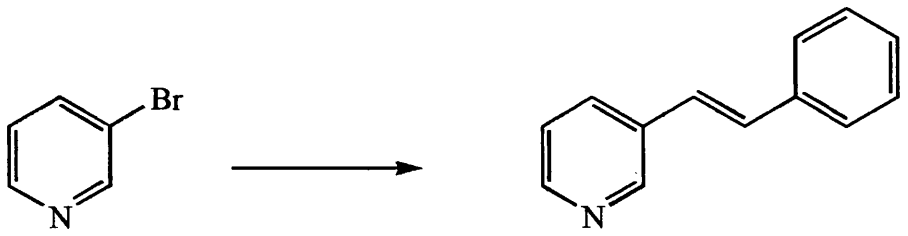
***N*-tert-Butoxycarbonyl-5-bromoindole, 76** (0.297 g, 1 mmol) was also used in the above experiment to give the product after 16 h reflux. Pd (<0.01 mg, <0.1%). The crude was subjected to deprotection.

Deprotection to give (*E*)-Methyl 3-(5-indolyl)acrylate, 78



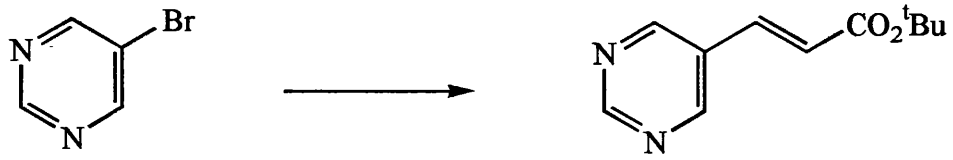
To a 50 ml round bottomed flask was added indole **77** (0.158 g, 0.52 mmol). A solution of trifluoroacetic acid (0.08 ml, 1.05 mmol) in dichloromethane (5 ml) was introduced to the flask. The reaction mixture was stirred under a nitrogen pressure at r.t. for 3 h. The solvent was removed *in vacuo* to give the *title compound* **78** as a colourless crystalline solid (0.103 g, 52%); Pd (<0.01 mg, <0.1%). See **78** for full analysis.

Typical synthesis of 3-Stilbazole, 80



A mixture of 3-bromopyridine **79** (0.16 g, 1 mmol), styrene **70** (0.14 ml, 1.25 mmol), Beads **E*i*** (375 mg, $Pd(OAc)_2$ (0.01 mmol, 1 mol%), ligand (0.04 mmol)) and triethylamine (0.42 ml, 3 mmol) was heated under reflux until TLC (light petroleum/ethyl acetate, 2:1) showed the reaction had gone to completion (25 h). The reaction mixture was cooled and was diluted with water (25 ml) and dichloromethane (50 ml). After washing with water (3 x 25 ml) the organic layer was dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue purified by "flash" column chromatography (eluant, light petroleum/ether, 4:1) to give the *title compound* **80** as a colourless crystalline solid (0.140 g, 77%); Pd (<0.01 mg, 0.1%); mp 79-81 °C (lit., [183] mp 80-82.5 °C); (Found: C, 86.4; H, 6.1; N, 7.5. $C_{13}H_{11}N$ requires C, 86.2; H, 6.1; N, 7.7%); (Found: M^+, 181.0890. $C_{13}H_{11}N$ requires 181.0891); ν_{max} (CH_2Cl_2)/cm^{-1} 3025 (Ar), 1566 (C=N), and 964 (CH=CH *trans*); δ_H 8.72 (1 H, d, $J_{H2,H4}$ 2.2, py ring H_2), 8.48 (1 H, dd, $J_{H5,H6}$ 4.7, py ring H_6), 7.83 (1 H, dt, $J_{H4,H5}$ 7.9, $J_{H2,H4}$ 2.2, py ring H_4), 7.55-7.26 (6 H, m, containing (5 H, Ar<u>H</u>) and (1 H, $J_{H4,H5}$ 7.9, $J_{H5,H6}$ 4.7, $J_{H2,H5}$ 2.2, py ring H_5), 7.17 (1 H, d, *J* 16.4, C<u>H</u>=CH), and 7.07 (1 H, d, *J* 16.4, CH=C<u>H</u>); δ_C (100.4 MHz; $CDCl_3$) 148.5 (Py ring C2 and C6), 136.6 (Ar<u>C</u>), 133.0 (Py ring C3 and C4), 130.8 (<u>C</u>H=), 128.8 (Ar C3' and C5'), 128.2 (Ar C4'), 126.6 (Ar C2' and C6'), 124.8 (=<u>C</u>H), and 123.5 (Py ring C5); *m/z* (EI) 180 (M^+, 100%), 166 (8), 152 (13), 90 (7), 76 (7), and 51 (7).

Typical synthesis of (2*E*)-1,1-Dimethylethyl -3-(5-pyrimidinyl) 2-propenoate, 83



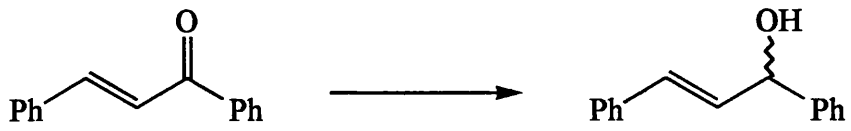
A mixture of 5-bromopyrimidine **81** (0.16 g, 1 mmol), Beads **C** ($Pd(OAc)_2$ (23 mg, 0.1 mmol, 10 mol%)), triethylamine (0.20 ml, 1.4 mmol), *tert*-butyl acrylate **82** (0.18 ml, 1.25 mmol) and toluene (5 ml) was stirred at 80 °C in a pressure tube for 48 h until complete as indicated by TLC (light petroleum/ether, 1:2). After cooling the reaction mixture was evaporated *in vacuo* to remove the excess *tert*-butyl acrylate and the residue recrystallised from hexane to give the *title compound* **83** as a colourless crystalline solid (0.137 g, 66%); Pd (<0.01 mg, <0.1%); mp 116.0-116.2 °C (lit., [126] mp 117.2-117.4 °C); (Found: C, 64.4; H, 7.0; N, 13.3. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%); (Found: M^+, 207.1135 (FABMS (M+H)). $C_{11}H_{15}N_2O_2$ requires 207.1089); ν_{max} (CH_2Cl_2)/cm^{-1} 2977 (CH_3), 1699 (CO), 1642, 1556 (C=N), 1233, 1155 (CO), and 988 (CH=CH *trans*); δ_H (250 MHz; $CDCl_3$) 9.11 (1 H, s, H_2), 8.80 (2 H, s, H_4 and H_6), 7.44 (1 H, d, *J* 16.1, C<u>H</u>=CHCO$_2$(CH_3)$_3$), 6.46 (1 H, d, *J* 16.1, =C<u>H</u>CO$_2$(CH_3)$_3$), and 1.47 (9 H, s, ($C\underline{H}_3$)$_3$); δ_C (100.4 MHz; $CDCl_3$) 164.9 (<u>C</u>O), 159.0 (C2), 155.5 (C4 and C6), 136.0 (<u>C</u>H=CHCO$_2$(CH_3)$_3$), 128.5 (C5), 124.3 (=<u>C</u>HCO$_2$(CH_3)$_3$), 81.5 (<u>C</u>(CH_3)$_3$), and 28.1 ($C\underline{H}_3$)$_3$); *m/z* (EI) 206 (M^+, 6%), 151 (100), 133 (87), 122 (6), 105 (10), and 78 (14).

5.4 Chapter 3 experimental

Experimental procedures

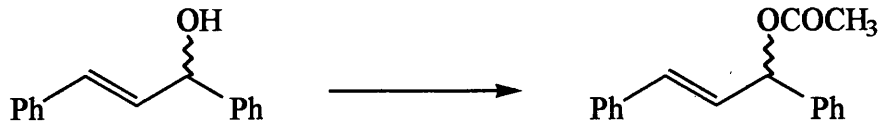
5.4.1 Allylic Substitution reactions

(*E*)-1,3-Diphenylprop-2-en-1-ol, 101



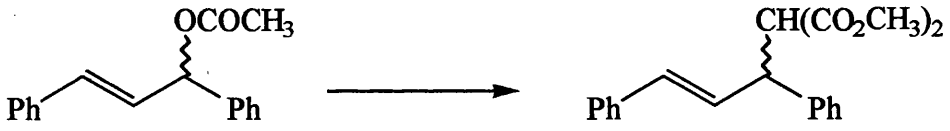
To a 100 ml three-armed round bottomed flask was added cerium chloride (III) heptahydrate (3.94 g, 10.50 mmol) and methanol (20 ml) was introduced by syringe. The reaction mixture was stirred at r.t. under a nitrogen atmosphere until homogeneous. Chalcone **100** (2 g, 9.60 mmol) was introduced to the flask. Again the flask was stirred at r.t. under a nitrogen pressure. Sodium borohydride (0.40 g, 10.50 mmol) was added slowly over a period of 30 min. The reaction mixture was stirred continuously under a nitrogen atmosphere, and monitored by TLC (light petroleum/ether, 3:1), until the reaction had gone to completion (2 h). The reaction was allowed to cool and then water was added dropwise to dissolve any residual sodium borohydride. Ethyl acetate (50 ml) was introduced and the organic layer was separated, washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a yellow oil. Purification by "flash" column chromatography (eluant, light petroleum/ether, 3:1) gave the *title compound* **101** as a colourless solid (1.708 g, 85%); mp 75-77 °C; δ_H (250 MHz; $CDCl_3$) 7.58-7.17 (10 H, m, ArH), 6.64 (1 H, d, *J* 15.8, PhCH=CH), 6.32 (1 H, dd, *J* 15.8, 6.4, CH=CHPh), 5.31 (1 H, d, *J* 6.4, CHPh), and 2.46 (1 H, br s, OH); δ_C (62.5 MHz; $CDCl_3$) 143.5 (ArC), 136.7 (ArC), 131.5 (CH=CH), 130.5 (CH=CH), 128.6 (ArCH), 128.5 (ArCH), 127.8 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 126.4 (ArCH), and 75.1 (CHPh).

(*E*)-1,3-Diphenyl-3-acetoxy-1-propene, 92



A solution of alcohol **101** (1.65 g, 7.88 mmol), triethylamine (1.65 ml, 11.83 mmol) and DMAP (2 mol%) in dichloromethane (20 ml) was stirred at 0 °C under a nitrogen pressure. Acetic anhydride (0.82 ml, 8.67 mmol) was added dropwise by syringe over a 30 min. period. After the addition was complete the reaction was allowed to warm to r.t. and after 2 h TLC analysis (light petroleum/ether, 3:1) indicated that all of the starting material had been consumed. The reaction mixture was washed with 2M sodium hydroxide solution (10 ml), and water (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a pale yellow oil (1.979 g, 99%); δ_H (250 MHz; $CDCl_3$) 7.42-7.21 (10 H, m, ArH), 6.63 (1 H, d, *J* 15.6, PhCH=CH), 6.44 (1 H, dd, *J* 15.6, 6.9, CH=CHPh), 6.34 (1 H, d, *J* 6.9, CHOCOCH$_3$), and 2.12 (3 H, s, OCOCH$_3$); δ_C (62.5 MHz; $CDCl_3$) 169.9 (CO), 139.2 (ArC), 136.1 (ArC), 132.5 (CH=CH), 128.6 (CH=CH), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 126.7 (ArCH), 76.1 (CHPh), and 21.3 (OCOCH$_3$).

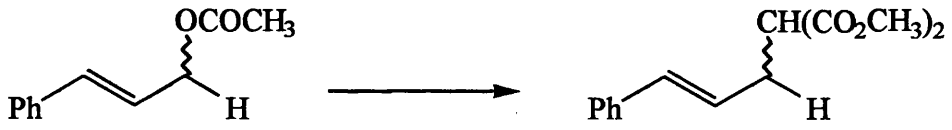
Typical synthesis of Dimethyl (1,3-Diphenylprop-2-enyl)malonate, 104



A solution of allylic acetate **92** (0.1 g, 0.4 mmol) and Beads **C** ($Pd(OAc)_2$ (2.7 mg, 0.01 mmol, 2.5 mol%), ligand **8** (0.04 mmol)) were dissolved in toluene (1 ml) and stirred at 20 °C for 15 min. under a nitrogen pressure. A solution of phosphazene base **102** (0.37 ml, 1.2 mmol), anhydrous sodium acetate (1 mg, 0.012 mmol, 3 mol%) and dimethyl malonate **103** (0.137 ml, 1.2 mmol) in toluene (1 ml) was then added and the reaction mixture stirred under reflux until TLC analysis (light petroleum/ether, 3:1) indicated that all of the starting material had been consumed (120 h). The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (10ml)

and extracted with dichloromethane (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a brown oil. Purification by "flash" column chromatography (eluant, light petroleum/ether, 5:1) gave the *title compound* **104** as a pale yellow solid (0.066 g, 51%); Pd (<0.01 mg, <0.1%); δ_H (250 MHz; $CDCl_3$) 7.40-7.10 (10 H, m, ArH), 6.48 (1 H, d, *J* 15.8, HC=CHPh), 6.33 (1 H, dd, *J* 15.8, 8.6, HC=CHPh), 4.27 (1 H, dd, *J* 10.9, 8.6, PhCH), 3.95 (1 H, d, *J* 10.9, $CHCO_2CH_3$), 3.70 (3 H, s, CH_3CO_2), and 3.52 (3 H, s, CH_3CO_2); δ_C (100.4 MHz; $CDCl_3$) 168.1 (CO), 167.7 (CO), 140.1 (ArC), 136.8 (ArC), 131.8 (HC=CAr) , 129.1 (ArCH), 128.7 (ArCH), 128.4 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 126.3 (ArCH), 57.6 ($CH(CO_2Me)_2$), 52.4 (CH_3CO_2), 52.6 (CH_3CO_2), and 49.1 (CHPh).

Typical synthesis of Methyl 2-carbomethoxy-5-phenylpent-4-enoate, 107



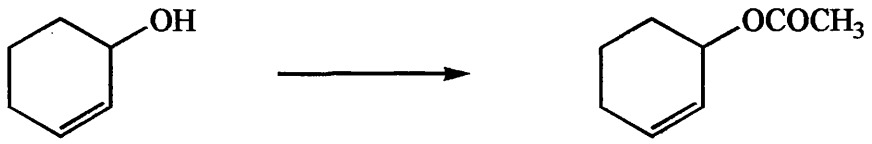
A solution of cinnamyl acetate **106** (0.070 g, 0.4 mmol) and Beads **C** ($Pd(OAc)_2$ (2.7 mg, 0.01 mmol, 2.5 mol%), ligand **8** (0.04 mmol)) were dissolved in toluene (1 ml) and stirred at 20 °C for 15 min. under a nitrogen pressure. A solution of phosphazene base **102** (0.37 ml, 1.2 mmol), anhydrous sodium acetate (1 mg, 0.012 mmol, 3 mol%) and dimethyl malonate **103** (0.137 ml, 1.2 mmol) in toluene (1 ml) was then added and the reaction mixture stirred under reflux until TLC analysis (light petroleum/ether, 3:1) indicated that all of the starting material had been consumed (48 h). The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (10 ml) and extracted with dichloromethane (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a brown oil. Purification by "flash" column chromatography (eluant, light petroleum/ether, 5:1) gave the *title compound* **107** as a colourless oil (0.091 g, 92%); Pd (<0.01 mg, <0.1%); δ_H (400 MHz; $CDCl_3$) 7.34-7.21 (5 H, m, ArH), 6.60 (1 H, d, *J* 15.9, $ArHC=CHCH_2$), 6.13 (1 H, dt, *J* 15.6, 7.0, $ArHC=CHCH_2$), 3.74 (6 H, s, OCH_3), 3.52 (1 H, t, *J* 7.0, $CH(CO_2Me)_2$), and 2.81

(2 H, dt, *J* 7.3, $C\underline{H}_2CO_2$); δ_C (100.4 MHz; $CDCl_3$) 169.3 ($\underline{C}O$), 137.0 (Ar$\underline{C}$), 133.0 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H) , 127.4 (Ar$\underline{C}$H), 126.2 (Ar$\underline{C}$H), 125.4 (Ar$\underline{C}$H), 52.6 ($\underline{C}H_3CO_2$), and 51.7 ($\underline{C}H(CO_2Me)_2$.

Typical synthesis of 3-Allyl-pentane-2,4-dione, 109

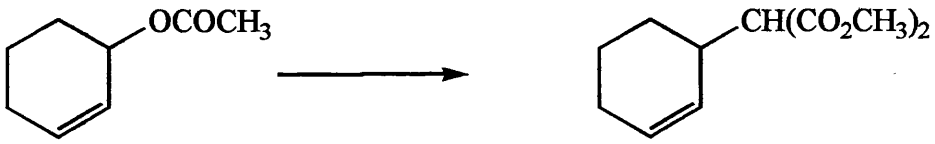
A solution of allyl acetate **108** (0.04 ml, 0.4 mmol) and Beads **C** ($Pd(OAc)_2$ (2.7 mg, 0.01 mmol, 2.5 mol%), ligand **8** (0.04 mmol)) were dissolved in toluene (1 ml) and stirred at 20 °C for 15 min. under a nitrogen pressure. A solution of phosphazene base **102** (0.37 ml, 1.2 mmol), anhydrous sodium acetate (1 mg, 0.012 mmol, 3 mol%) and dimethyl malonate **103** (0.137 ml, 1.2 mmol) in toluene (1 ml) was then added and the reaction mixture stirred under reflux until TLC analysis (light petroleum/ether, 3:1) indicated that all of the starting material had been consumed (6 h). The reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (10 ml) and extracted with dichloromethane (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a brown oil. Purification by "flash" column chromatography (eluant, light petroleum/ether, 5:1) gave the *title compound* **109** as a colourless oil (0.041 g, 59%); Pd (<0.01 mg, <0.1%); δ_H (250 MHz; $CDCl_3$) 5.85-5.70 (1 H, ddt, *J* 10.6, 7.0, =C$\underline{H}$CH$_2$), 5.15 (1 H, dd, *J* 15.6, 1.6, C$\underline{H}$H=CH), 5.07 (1 H, dd, *J* 10.8, 1.6, CH$\underline{H}$=CH), 3.74 (6 H, s, OC$\underline{H}_3$), 3.48 (1 H, t, *J* 7.5, C$\underline{H}CO_2CH_3$), and 2.64 (2 H, dd, *J* 7.3, 7.0, =CHC$\underline{H}_2$); δ_C (67.80 MHz; $CDCl_3$) 169.2 ($\underline{C}O$), 133.8 (=$\underline{C}HCH_2$), 117.5 ($\underline{C}H_2$=$CHCH_2$), 52.4 ($\underline{C}HCO_2CH_3$), 51.3 (O$\underline{C}H_3$), and 32.8 ($\underline{C}H_2$).

Cyclohex-2-enyl acetate, 111



To a 50 ml round bottomed flask was added 2-cyclohexen-1-ol **110** (1 g, 0.01 mol), a few crystals of DMAP and dichloromethane (30 ml). Triethylamine (2.1 ml, 0.015 mol) was added by syringe. The solution was cooled to 0 °C with an ice bath under a nitrogen pressure and acetic anhydride (1.0 ml, 0.01 mol) was added dropwise by syringe over a period of 30 min. The reaction was allowed to warm to r.t. and reaction was monitored by TLC. The reaction had gone to completion after 2 h. The reaction solvent was removed *in vacuo* and the product purified by "flash" column chromatography (eluant, light petroleum/ether 3:1), to give the *title compound* **111** as a colourless oil (0.97 g, 68%); δ_H (250 MHz; $CDCl_3$) 5.88-5.81 (1 H, dt, *J* 10.1, 3.7, C<u>H</u>=CHC), 5.62-5.58 (1 H, br d, *J* 10.1, CH=C<u>H</u>C), 5.16 (1 H, br s, C<u>H</u>OCOCH$_3$), 2.18 (3 H, s, C<u>H</u>$_3$) and 1.97-1.54 (6 H, m, C<u>H</u>$_2$ x 3); δ_C (67.80 MHz; $CDCl_3$) 170.4 (<u>C</u>O), 132.3 (=<u>C</u>H), 125.5 (<u>C</u>H=), 67.8 (<u>C</u>H), 28.0 (<u>C</u>H$_2$), 24.6 (<u>C</u>H$_2$), 21.0 (<u>C</u>H$_3$) and 18.6 (<u>C</u>H$_2$).

Typical synthesis of Dimethyl cyclohex-2-enylmalonate, 112



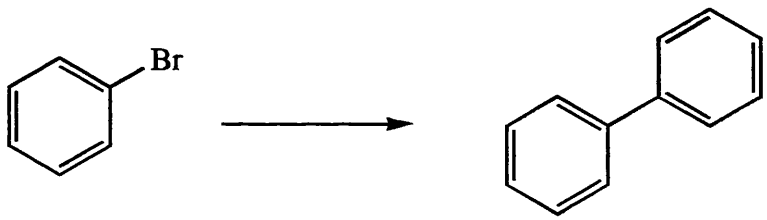
A solution of 2-cyclohexenyl acetate **111** (0.06 g, 0.4 mmol) and Beads **C** $(Pd(OAc)_2$ (2.7 mg, 0.01 mmol, 2.5 mol%), ligand **8** (0.04 mmol)) were dissolved in toluene (1 ml) and stirred at 20 °C for 15 min. under a nitrogen pressure. A solution of phosphazene base **102** (0.37 ml, 1.2 mmol), anhydrous sodium acetate (1 mg, 0.012 mmol, 3 mol%) and dimethyl malonate **103** (0.137 ml, 1.2 mmol) in toluene (1 ml) was added and the reaction mixture heated under reflux until TLC analysis

(light petroleum/ether, 3:1) indicated that all of the starting material had been consumed (16 h). The reaction mixture was quenched with a saturated solution of ammonium chloride (10 ml) and extracted with dichloromethane (2 x 20 ml). The organic layers were combined, washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding a brown oil. Purification by "flash" column chromatography (eluant, light petroleum/ether, 3:1) gave the *title compound* **112** as a colourless oil (0.050 g, 59%); Pd (<0.01 mg, 0.1%); δ_H (250 MHz; $CDCl_3$) 5.69-5.62 (1 H, dt, *J* 10.1, 2.2, C<u>H</u>=CHC), 5.42-5.37 (1 H, dd, *J* 10.1, 2.2, CH=C<u>H</u>C), 3.62 (3 H, s, C<u>H</u>$_3$ x 2), 3.17 (1 H, d, C<u>H</u>CO_2CH_3), 2.82-2.74 (1 H, m, C<u>H</u>), and 1.97-1.54 (6 H, m, C<u>H</u>$_2$ x 3); δ_C (67.80 MHz, $CDCl_3$) 168.8 (<u>C</u>O), 129.6 (=<u>C</u>H), 127.3 (<u>C</u>H=), 56.8 (<u>C</u>H), 52.3 (<u>C</u>H), 35.3 (<u>C</u>H$_3$), 26.6 (<u>C</u>H$_2$), 24.9 (<u>C</u>H$_2$), and 20.8 (<u>C</u>H$_2$).

5.4.2 Suzuki Coupling reactions

Experimental procedures

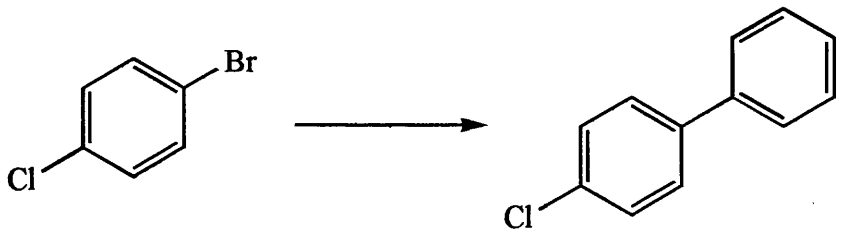
Typical synthesis of Biphenyl, 126



To a 50 ml round bottomed flask was added Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)). Bromobenzene **51** (0.26 ml, 2.48 mmol), toluene (5 ml) and an aqueous solution (2 M) of sodium bicarbonate (2.48 ml, 4.96 mmol) was added. Phenylboronic acid **114** (0.33 g, 2.73 mmol) in ethanol (1ml) was introduced to the flask. The reaction mixture was heated under reflux with vigorous stirring under a nitrogen pressure until reaction had gone to completion (5 h). After the reaction was complete the catalyst was separated from the reaction mixture (by decantation). The supernatant was introduced into a 50 ml round bottomed flask where it was subjected to 30% hydrogen peroxide (0.1 ml) to oxidise any residual phenylboronic acid at r.t. for 1 h. The product was extracted with ether, washed with saturated ammonium chloride

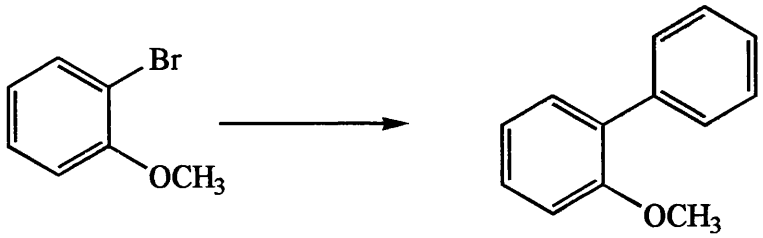
solution (3 x 25 ml), dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield the *title compound* **126** as a pale yellow crystalline solid (0.33 g, 87%); Pd (<0.01 mg, 0.1%); mp 69-72 °C (lit.,[180] mp 70-72 °C); δ_H (250 MHz; $CDCl_3$) 7.65-7.24 (10 H, m, ArH).

Typical synthesis of 4-Chlorobiphenyl, 128



To a 50 ml round bottomed flask was added Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)). 4-Bromochlorobenzene **127** (0.47 g, 2.48 mmol), toluene (5 ml) and an aqueous solution (2 M) of sodium bicarbonate (2.48 ml, 4.96 mmol) was added. Phenylboronic acid **114** (0.33 g, 2.73 mmol) in ethanol (1ml) was introduced to the flask. The reaction mixture was heated under reflux with vigorous stirring under a nitrogen pressure until reaction had gone to completion (4 h). After the reaction was complete the catalyst was separated from the reaction mixture (by decantation). The supernatant was introduced into a 50 ml round bottomed flask where it was subjected to 30% hydrogen peroxide (0.1 ml) to oxidise any residual phenylboronic acid at r.t. for 1 h. The product was extracted with ether, washed with saturated ammonium chloride solution (3 x 25 ml), dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield the *title compound* **128** as a colourless crystalline solid (0.497 g, 86%); Pd (<0.01 mg, 0.1%); mp (76-78 °C); δ_H (250 MHz; $CDCl_3$) 7.61-7.40 (9 H, m, ArH).

Typical synthesis of 2-Methoxybiphenyl, 130



To a 50 ml round bottomed flask was added Beads **D** (88.5 mg, $PdCl_2$ (0.02 mmol, 1 mol%)). 2-Bromoanisole **129** (0.31 ml, 2.48 mmol), toluene (5 ml) and an aqueous solution (2 M) of sodium bicarbonate (2.48 ml, 4.96 mmol) was added. Phenylboronic acid **114** (0.33 g, 2.73 mmol) in ethanol (1ml) was introduced to the flask. The reaction mixture was heated under reflux with vigorous stirring under a nitrogen pressure until reaction had gone to completion (7 h). After the reaction was complete the catalyst was separated from the reaction mixture (by decantation). The supernatant was introduced into a 50 ml round bottomed flask where it was subjected to 30% hydrogen peroxide (0.1 ml) to oxidise any residual phenylboronic acid at r.t. for 1 h. The product was extracted with ether, washed with saturated ammonium chloride solution (3 x 25 ml), dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* to yield the *title compound* **130** as a colourless crystalline solid (0.434 g, 95%); Pd (<0.01 mg, 0.2%); mp 31-32 °C (lit.,[180] 30-33 °C); δ_H (250 MHz; $CDCl_3$) 7.58-6.70 (9 H, m, Ar<u>H</u>), 3.85 (3 H, s, OC<u>H</u>$_3$).

Test for palladium

General procedure

These tests were performed to try to establish whether the palladium lies in the organic or aqueous layer during the Suzuki coupling reaction.

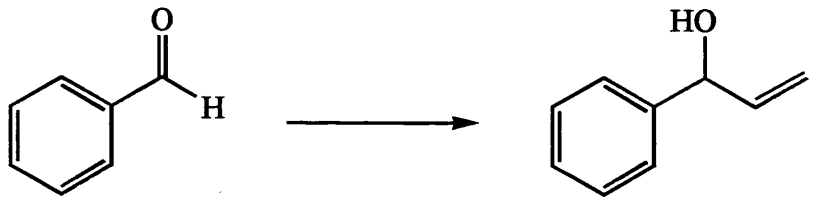
Palladium chloride (8.8 mg, 0.05 mmol, 1 mol%), TPPTS **8** (62 mg, 0.11 mmol, 2.2 eq.), ethylene glycol (1 drop), triphenylphosphine (28.6 mg, 0.11 mmol, 2.2 eq.), Davisil 500Å (100 mg), toluene (10 ml) and water (10 ml) were introduced into a separatory funnel. The mixture was shaken in a separatory funnel and the two layers extracted. The organic sample was concentrated under reduced pressure and aqua

regia added to extract palladium. The aqueous sample was used directly in palladium analysis. The dilution factor was taken into account in each case. Pd (organic: 0.04 mg, 0.7%, aqueous: 5.24 mg, 99.2%).

5.4.3 Allylic acetate rearrangement reactions

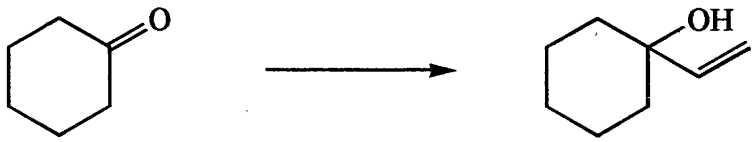
Experimental procedures

1-Phenylallyl alcohol (1-phenyprop-2-en-1-ol), 145



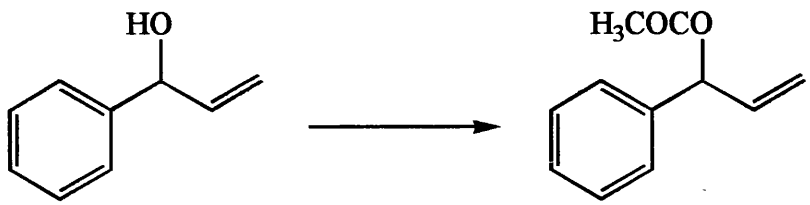
A solution of benzaldehyde **143** (3 g, 28.27 mmol) and dry THF (30 ml) was introduced to a 150 ml round-bottomed flask and cooled to -78 °C under a nitrogen atmosphere. A 1 M solution of vinyl magnesium bromide **144** in THF (34.0 ml, 33.92 mmol, 1.2 eq.) was added slowly by syringe to the aldehyde whilst stirring over a 30 min. period. The reaction mixture was warmed slowly to r.t. and stirred for a further 3 h until the reaction had gone to completion. The reaction was then quenched with aqueous ammonium chloride solution, diluted with ether and washed with distilled water. The mixture was introduced to a 250 ml separating flask and brine was added to form two distinct layers. The aqueous layer was extracted with ether (3 x 30 ml). The etherate was dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and purified by "flash" column chromatography (eluant, light petroleum/ether, 4:1) to give the *title compound* **145** as a colourless viscous oil (3.00 g, 80% yield); ν_{max} (neat)/cm^{-1} 3370 (OH), 1033, 991 ($RCH=CH_2$), 929 ($RCH=CH_2$), 760, and 700; δ_H (250 MHz; $CDCl_3$) 7.1-7.4 (5 H, m, ArH), 5.98 (1 H, ddd, *J* 17.1, 10.2, 6.1, $CH=CH_2$), 5.27 (1 H, br d, *J* 17.1, CH=CHH), 5.13 (1 H, br d, *J* 10.2, CH=CHH), 5.11 (1 H, d, *J* 6.1, CHOH), and 2.36 (1 H, br s, CHOH).

1-Vinyl cyclohexanol (1-ethenylcyclohexanol), 148



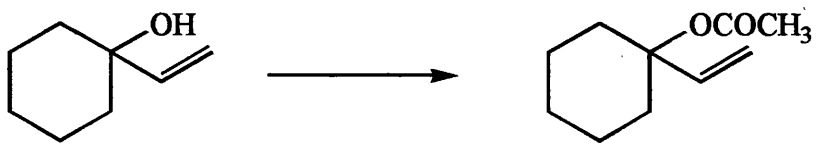
A solution of cyclohexanone **147** (2 g, 20.38 mmol) and dry ether (20 ml) were introduced to a 150 ml round-bottomed flask and cooled to -78 °C under a nitrogen atmosphere. A 1 M solution of vinyl magnesium bromide **144** in THF (2.45 ml, 24.45 mmol, 1.2 eq.) was added slowly by syringe to the ketone whilst stirring over a 30 min. period. The reaction mixture was warmed slowly to r.t. and stirred for a further 3 h until reaction had gone to completion. The reaction mixture was then quenched with aqueous ammonium chloride solution, diluted with ether and washed with distilled water. The mixture was introduced to a 250 ml separating flask and brine was added to form two distinct layers. The aqueous layer was extracted with ether (3 x 30 ml). The etherate was dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and purified by "flash" column chromatography (eluant, light petroleum/ether, 4:1) to yield the *title compound* **148** as a colourless viscous oil (1.031 g, 36% yield); bp 70 ° (14 mm Hg) [lit., [184] bp 67-68 ° (10 mm Hg)]; $\nu_{max.}$ (neat)/cm^{-1} 3422 (OH), 2933, 1642, 1466, and 966 ($RCH=CH_2$), 916; δ_H (250 MHz, $CDCl_3$) 5.94 (1 H, dd, *J* 17.4, 10.8, C<u>H</u>=CH_2), 5.22 (1 H, dd, *J* 17.4, 1.5, CH=C<u>H</u>H), 4.99 (1 H, dd, *J* 10.8, 1.5, CH=CH<u>H</u>), 4.00 (1 H, s, CHO<u>H</u>) and 1.0-1.8 (11 H, m, C<u>H</u>$_2$ x 4 and C<u>H</u>OH); δ_C (67.8 MHz; $CDCl_3$) 145.9 (<u>C</u>H=CH_2), 111.2 (CH=<u>C</u>H_2), 71.4 (<u>C</u>HOH), 37.3 (<u>C</u>H_2), 25.4 (<u>C</u>H_2 x 2), and 21.8 (<u>C</u>H_2 x 2).

1-Phenylprop-2-enyl acetate (1-acetoxy-1-phenylprop-2-ene), 146



To a 100 ml round-bottomed flask was added alcohol **145** (2.9 g, 21.64 mmol), dichloromethane (30 ml), triethylamine (4.5 ml, 32.46 mmol, 1.5eq.) and a few crystals of DMAP. The flask was cooled to 0 °C using an ice-bath under a nitrogen pressure. Acetic anhydride (2.25 ml, 23.81 mmol, 1.1eq.) was introduced dropwise into the flask over a 30 min. period. The flask was warmed to r.t. and the reaction mixture stirred for a further 4 h until the reaction had gone to completion. The reaction mixture was concentrated *in vacuo* and purified using "flash" column chromatography (eluant, light petroleum/ether, 4:1) to yield the *title compound* **146** as a colourless viscous oil (3.138 g, 82%); $\nu_{max.}$ (neat)/cm^{-1} 3066, 3032, 2933, 1741 ($OCOCH_3$), 1604, 1451, 1371, 1097 (CO), 936 ($RCH=CH_2$), 845, and 736; δ_H (250 MHz; $CDCl_3$) 7.38 (5 H, m, Ar<u>H</u>), 6.35 (1 H, d, *J* 5.9, C<u>H</u>$OCOCH_3$), 6.05 (1 H, ddd, *J* 17.2, 10.4, 5.9, C<u>H</u>$=CH_2$), 5.33 (1 H, br d, *J* 17.2, CH=C<u>H</u>$_2$), 5.26 (1 H, br d, *J* 10.4, CH=C<u>H</u>$_2$), and 2.09 (3 H, s, $OCOCH_3$).

1-Vinylcyclohexyl acetate, 149



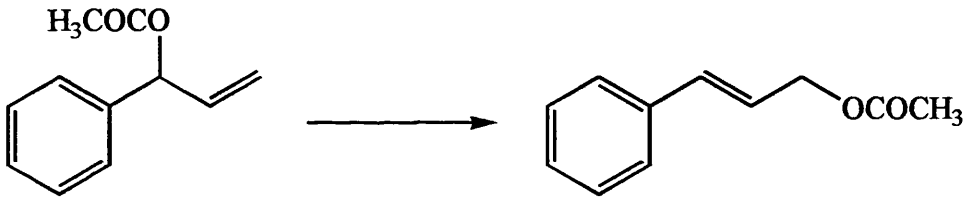
To a 100 ml round-bottomed flask was added alcohol **148** (0.5 g, 3.60 mmol), dichloromethane (10 ml), triethylamine (0.75 ml, 5.40 mmol, 1.5eq.) and a few crystals of DMAP. The flask was cooled to 0 °C using an ice-bath under a nitrogen pressure. Acetic anhydride (0.37 ml, 3.96 mmol, 1.1eq.) was introduced dropwise into the flask over a 30 min. period. The flask was warmed to r.t. and the reaction mixture stirred for a further 4 h until the reaction had gone to completion. The reaction mixture was

concentrated *in vacuo* and purified using "flash" column chromatography (eluant, light petroleum/ether, 4/1) to yield the *title compound* **149** as a colourless viscous oil (0.292 g, 48%); bp 65 ° (1mmHg); $\nu_{max.}$ (neat)/cm^{-1} 1735 ($OCOCH_3$), 1640, 1235 (CO), 990 ($RCH=CH_2$), and 913; δ_H (250 MHz; $CDCl_3$) 5.94 (1 H, dd, *J* 17.4, 10.8, C<u>H</u>=CH_2), 5.22 (1 H, dd, *J* 17.4, 1.5, CH=C<u>H</u>H), 4.99 (1 H, dd, *J* 10.8, 1.5, CH=CH<u>H</u>), 2.35 (4 H, m, $C\underline{H}_2$ x 2), 2.12 (3 H, s, $OC\underline{H}_3$), 1.50 (4 H, m, $C\underline{H}_2$ x 2), and 1.48 (1 H, m, $C\underline{H}_2$); δ_C (68.80 MHz, $CDCl_3$) 141.7 (<u>C</u>H=CH_2), 113.2 (CH=<u>C</u>H_2), 81.4 ($O\underline{C}OCH_3$), 34.6 ($\underline{C}H_2$ x 2), 25.1 ($O\underline{C}H_3$), 25.1 ($\underline{C}H_2$) and 21.6 ($\underline{C}H_2$ x 2).

Bis(acetonitrile) dichloride palladium (II)[185]

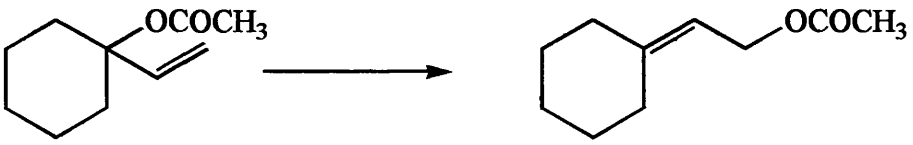
Palladium chloride (200 mg) was heated to reflux in acetonitrile until a clear solution was obtained (@ 1h). This solution was then filtered hot and reduced to a small volume *in vacuo*. The product was filtered, washed with ether and dried *in vacuo* to yield a bright yellow solid (0.258 g, 88%).

Typical synthesis of Cinnamyl acetate, 150



The allylic acetate **146** (100 mg, 0.57 mmol), Beads **C** ($PdCl_2$ (2 mg, 0.01 mmol, 1 mol%)) and hexane/ether, 2:1 (3 ml) were introduced into a 50 ml round-bottomed flask. The reaction was carried out at r.t. under a nitrogen pressure and monitored by GC until the product was formed (24 h). The reaction mixture was filtered, concentrated *in vacuo* and distilled by kugelrohr bp 70 °C (14mm Hg) to give the *title compound* **150** as a viscous yellow oil (40.5% conversion); Pd (<0.01 mg, 1.35%); δ_H (250 MHz; $CDCl_3$) 7.24 (5 H, m, Ar<u>H</u>), 6.57 (1 H, br d, *J* 15.9, C<u>H</u>=CH), 6.23 (1 H, dt, *J* 15.9, 6.4, CH=C<u>H</u>), 4.65 (2 H, dd, *J* 6.4, 1.3, CH=CHC<u>H</u>$_2$), and 2.02 (3 H, s, $OC\underline{H}_3$).

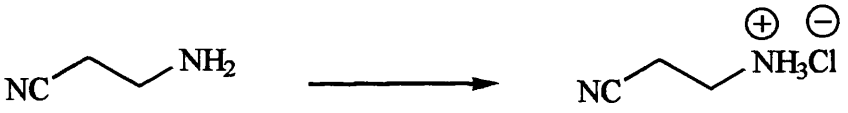
Typical synthesis of 2-Ethylidenecyclohexyl acetate, 156



The allylic acetate **149** (100 mg, 0.57 mmol), Beads **C** ($PdCl_2$ (7 mg, 0.04 mmol, 4 mol%)) and hexane/ether, 2:1 (3 ml) were introduced into a 50 ml round-bottomed flask. The reaction was carried out at r.t. under a nitrogen pressure and monitored by GC until the product was formed (72 h). The reaction was filtered and concentrated *in vacuo* to give the *title compound* **156** as a viscous yellow oil (47% conversion); δ_H (250 MHz; $CDCl_3$) 5.40 (1 H, m, C<u>H</u>=C), 5.17 (1 H, m, C<u>H</u>$_2$O), and 2.04 (3 H, s, OCOC<u>H</u>$_3$), and 1.80-1.64 (10 H, m, C<u>H</u>$_2$ x 5).

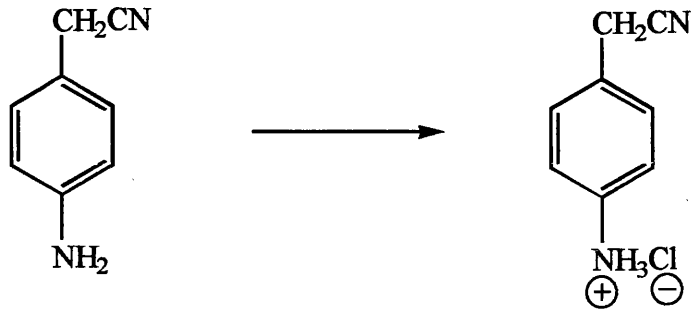
Synthesis of water-soluble ligands

Ammonium chloride salt of 3-aminopropionitrile fumarate, 153



Into a 50 ml round-bottomed flask, 3-aminopropionitrile fumarate **152** (1 g, 7.80 mmol) was added to ether (20 ml) to form a suspension. A 12 M solution of hydrochloric acid (0.65 ml, 7.80 mmol) was added dropwise over a 30 min. period whilst stirring. The reaction mixture was stirred at r.t for a further 30 min. and then filtered with ether. The solid was placed *in vacuo* to remove any trace solvent to afford a colourless flaky solid (0.54 g, 65%); δ_H (250 MHz; D_2O) 6.78 (3 H, s, ND_2<u>H</u>), 3.35 (2 H, t, C<u>H</u>$_2$CN), and 2.95 (2 H, t, RC<u>H</u>$_2$CH$_2$CN); δ_C (67.80 MHz, D_2O) 117.5 (<u>C</u>N), 35.0 (CN<u>C</u>H$_2$CH$_2$), and 15.5 (CNCH$_2$<u>C</u>H$_2$).

Ammonium chloride salt of 4-aminobenzyl cyanide, 155

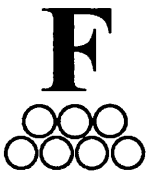


Into a 100 ml round-bottomed flask 4-aminobenzyl cyanide **154** (2 g, 16.37 mmol) was added to ether (30 ml) to form a suspension. A 12 M solution of hydrochloric acid (1.5 ml, 16.37 mmol) was added dropwise over a 30 min. period whilst stirring. The reaction mixture was stirred at r.t for a further 30 min. and washed with cold ethanol then filtered with ether. The solid was placed *in vacuo* to remove any trace solvent to afford a colourless solid (2.138 g, 82%); δ_H (250 MHz, D_2O) 7.40 (4 H, dd, Ar<u>H</u>), 4.90 (3 H, s, N<u>D</u>$_3$), and 3.90 (2 H, s, Ar<u>C</u>H$_2$CN); δ_C (67.80 MHz, D_2O) 132.6 (<u>C</u>NH$_3$Cl), 129.6 (Ar<u>C</u>H), 122.3 (ArCH$_2$<u>C</u>N), 22.1 (AR<u>C</u>H$_2$CN).

5.5 Chapter 4 experimental

Glass beads as sponges

Typical synthesis of the filter and its use as a "sponge"



In a typical preparation, to a 50 ml round-bottomed flask were introduced Davisil 500Å beads (1 g), TPPTS **8** (620 mg) and ethylene glycol (1 ml). The mixture was stirred at r.t. for 1 h. The so formed sponge beads were then added directly to the reaction mixture ("stir-in technique") and stirred for a few minutes. The organic solvent was then decanted off and tested for palladium.

Alternatively, the so formed sponge beads were added to a bond elut, compressed with a plunger ("filter technique") and the reaction mixture passed directly through the bed of beads into a test tube. The sample was collected and tested for palladium.

For the latter filtration experiments, the sponge beads were introduced to a sinter funnel (1 cm diameter, 10 cm length), packed and toluene was flushed through. The palladium solution (palladium acetate (50 mg) in toluene (10 ml)) was introduced and the filtered solution collected in aliquots (0.5 ml) and analysed for palladium.

REFERENCES

References

1. Herrmann, W.A. and Kohlpaintner, C.W., *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1524.
2. Brown, J.M. and Davis, S.G., *Nature*, 1994, **370**, 418.
3. Herrmann, W.A. and Cornils, B., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1048.
4. For reviews on catalytic applications using transition metals see a) Tonks, L. and Williams, J.M.J., *Contemporary Organic Synthesis*, 1997, **4**, 353. b) Tonks, L. and Williams, J.M.J., Specialist Periodical Reports, *Organomet. Chem.*, 1998, **26**, 180. c) Tonks, L. and Williams, J.M.J., *J. Chem. Soc., Perkin Trans. 1*, 1998, 3637. d) Tonks, L. and Williams, J.M.J., Specialist Periodical Reports, *Organomet. Chem.*, 1999, **27** (in press).
5. Davis, M.E., *CHEMTECH.*, 1992, 498.
6. a) Bumagin, N.A., Gulevich, Y.V. and Beletskaya, I.P., *J. Organomet. Chem.*, 1985, **285**, 415. b) Bumagin, N.A., Ponomaryov, A.B. and Beletskaya, I.P., *Tetrahedron Lett.*, 1985, **39**, 4819.
7. Cheprakov, A.V., Ponomareva, N.V. and Beletskaya, I.P., *J. Organomet. Chem.*, 1995, **486**, 297.
8. Bumagin, N.A., Nikitin, K.V. and Beletskaya, I.P., *J. Organomet. Chem.*, 1988, **358**, 563.
9. a) Horváth, I.T. and Rabái, J., *Science*, 1994, **266**, 72. b) Cornils, B., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2057.
10. a) Hughes, R.P. and Trujillo, H.A., *Organometallics*, 1996, **15**, 286. b) Pozzi, G., Banfi, S., Manfredi, A., Montanari, F. and Quici, S., *Tetrahedron*, 1996, **36**, 11879.
11. Juliette, J.J.J., Horváth, I.T. and Gladysz, J.A., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1610.
12. Klement, I., Lütjens, H. and Knochel, P., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1454.

13. a) Curran, D.P. and Hoshino, M., *J. Org. Chem.*, 1996, **61**, 6480. b) Curran, D.P. and Hadida, S., *J. Am. Chem. Soc.*, 1996, **118**, 2531. c) Larhed, M., Hoshino, M., Hadida, S., Curran, D.P. and Hallberg, A., *J. Org. Chem.*, 1997, **62**, 5583. d) Hoshino, M., Degenkolb, P. and Curran, D.P., *J. Org. Chem.*, 1997, **62**, 8341.
14. Cornils, B. and Kuntz, E.G., *J. Organomet. Chem.*, 1995, **502**, 177.
15. Joó, F. and Tóth, Z., *J. Mol. Catal.*, 1980, **8**, 369.
16. Arhancet, J.P., Davis, M.E., Merola, J.S. and Hanson, B.E., *Nature*, 1989, **339**, 454.
17. Tolman, C.A., *Chem. Rev.*, 1977, **77**, 313.
18. Roundhill, D.M., *Advances in Organometallic Chemistry*, 1994, **38**, 172.
19. Kiji, J., Okano, T., Nishuiri, W. and Konishi, H., *Chem. Lett.*, 1988, 957.
20. Okano, T., Morijama, Y., Konishi, H. and Kiji, J., *Chem. Lett.*, 1986, 1463.
21. a) Joó, F., Tóth, Z., Beck, M.T., *Inorg. Chim. Acta*, 1977, **25**, L 61. b) Osborn, J.A. and Wilkinson, G., *Chem. Commun.*, 1965, 17; *ibid*, 1965, 131.
22. Kuntz, E.G., *CHEMTECH.*, 1987, **17**, 570.
23. Grosselin, J.M., Mercier, C., Allmang, G. and Grass, F., *Organometallics*, 1991, **10**, 2126.
24. Joó, F., Csiba, P. and Bényei, A., *J. Chem. Soc., Chem. Commun.*, 1993, 1602.
25. Joó, F., Kovács, J., Bényei, A. and Kathó, A., *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 969.
26. Amatore, C., Blart, E., Genêt, J.P., Jutand, A., Lemaire-Audoire, S. and Savignac, M., *J. Org. Chem.*, 1995, **60**, 6829.
27. a) Herd, O., Langhans, K.P., Stelzer, O., Weferling, N. and Sheldrick, W.S., *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1058. b) Bitterer, F., Herd, O., Hessler, A., Kühnel, M., Rettig, K., Stelzer, O., Shledrick, W.S., Nagel, S. and Rösch, N., *Inorg. Chem.*, 1996, **35**, 4103.
28. Herdtweck, E., Peters, F. and Wagner, M., *Chem. Ber.*, 1997, **130**, 515.
29. a) Issleib, K. and Thomas, G., *Chem. Ber.*, 1960, **93**, 803. b) Issleib, K., Kümmel, R. and Zimmerman, H., *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 155.

30. a) Issleib, K. and Thomas, G., *Chem. Ber.*, 1961, **94**, 2244. b) Empsall, H.D., Hyde, E.M., Pawson, D. and Shaw, B.L., *J. Chem. Soc., Dalton Trans*, 1977, 1292.

31. Kalck, P. and Monteil, F., *Advances in Organometallic Chemistry*, 1992, **34**, 219.

32. Kosolapoff, W. and Maier, L., "*Organic phosphorus compounds*", Vol. 1, Wiley (Interscience), New York, 1972.

33. Smith, R.T. and Baird, M.C., *Inorg. Chim. Acta*, 1982, **62**, 135.

34. Smith, R.T., Ungar, R.K., Sanderson, L.J. and Baird, M.C., *Organometallics*, 1983, **2**, 1138.

35. Markiewicz, M.K. and Baird, M.C., *Inorg. Chim. Acta*, 1986, **113**, 95.

36. Tripett, S., *J. Chem. Soc.*, 1961, 2813.

37. a) Issleib, K. and Möbius, H.-M., *Chem. Ber.*, 1961, **94**, 102. b) Issleib, K. and Rockstroh, K., *Chem. Ber.*, 1963, **96**, 407. c) Issleib, K. and Roloff, H.R., *Chem. Ber.*, 1965, **98**, 2091.

38. Frémy, G., Castanet, Y., Grzybek, R., Monflier, E., Mortreux, A., Trzeciak, A.M. and Ziolkowski, J.J., *J. Organomet. Chem.*, 1995, **505**, 11.

39. Renaud, E., Russell, R.B., Forier, S., Brown, S.J. and Baird, M.C., *J. Organomet. Chem.*, 1991, **419**, 403.

40. Mercier, F. and Mathey, F., *J. Organomet. Chem.*, 1993, **462**, 103.

41. Avey, A., Schut, D.M., Weakley, T.J.R. and Tyler, D.R., *Inorg. Chem.*, 1993, **32**, 233.

42. Buhling, A., Elgersma, J.W., Nkrumah, S., Kamer, P.C.J. and van Leeuwan, P.W.N.M., *J. Chem. Soc., Dalton Trans.*, 1996, 2143.

43. a) Nuzzo, R.G., Feitler, D. and Whitesides, G.M., *J. Am. Chem. Soc.*, 1979, 3683. b) Nuzzo, R.G., Haynie, S.L., Wilson, M.E. and Whitesides, G.M., *J. Org. Chem.*, 1981, **46**, 2861.

44. Lelièvre, S., Mercier, F. and Mathey, F., *J. Org. Chem.*, 1996, **61**, 3531.

45. Herrmann, W.A., Kohlpaintner, C.W., Manetsberger, R.B., Bahrmann, H. and Kottmann, H., *J. Mol. Catal. A: Chemical*, 1995, **97**, 65.

46. Schull, T.L., Fettinger, J.C. and Knight, D.A., *J. Chem. Soc., Chem. Commun.*, 1995, 1487.

47. Früchtel, J.S. and Jung, G., *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 17.

48. a) Ajjou, A.N. and Alper, H., *J. Am. Chem. Soc.*, 1998, **120**, 1466. b) Tóth, I. and Hanson, B.E., *Tetrahedron: Asymmetry*, 1990, **1**, 895. c) Tóth, I., Hanson, B.E. and Davis, M.E., *Tetrahedron: Asymmetry*, 1990, **1**, 913.

49. Amrani, Y., Lecomte, L. and Sinou, D., *Organometallics*, 1989, **8**, 542.

50. a) Bartik, T., Bunn., B.B., Bartik, B. and Hanson, B.E., *Inorg. Chem.*, 1994, **33**, 164. b) Herrmann, W.A., Kohlpaintner, C.W., Bahrmann, H. and Konkol, W., *J. Mol. Catal.*, 1992, **73**, 191.

51. Tafesh, A.M. and Beller, M., *Tetrahedron Lett.*, 1995, **36**, 9305.

52. Malmström, T. and Andersson, C., *J. Chem. Soc., Chem. Commun.*, 1996, 1135.

53. For current reviews on solid-phase organic synthesis see a) Brown, R, *Contemporary Organic Synthesis*, 1997, **4**, 216. b) Hermkens, P.H.H., Ottenheijm, H.C.J. and Rees, D., *Tetrahedron*, 1996, **52**, 4527. c) Thompson, L.A. and Ellman, J.A., *Chem. Rev.*, 1996, **96**, 555.

54. Shuttleworth, S.J., Allin, S.M. and Sharma, P.K., *Synthesis*, 1997, 1217.

55. For an example of a Stille coupling in synthesis see Plunkett, M.J. and Ellman, J.A., *J. Am. Chem. Soc.*, 1995, *117*, 3306.

56. Deshpande, M.S., *Tetrahedron Lett.*, 1994, **35**, 5613.

57. Han, H. and Janda, K.D., *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1731.

58. Hintzen, B. and Ley, S.V., *J. Chem. Soc., Perkin Trans 1*, 1997, 1907; *ibid*, 1998, 1.

59. Gao, H. and Angelici, R.J., *J. Am. Chem. Soc.*, 1997, **119**, 6937.

60. Cai, M-Z., Song, C-S. and Huang, X., *J. Chem. Soc., Perkin Trans. 1*, 1997, 2273.

61. Cai, M-Z., Song, C-S. and Huang, X., *Synth. Commun.*, 1997, **27**, 3087.

62. Hartley, F.R, in "*Supported metal complexes*", Eds. Ugo, R and James, B.R., Reidel, New York, 1985.

63. Arhancet, J.P., Davis, M. E., Merola, J.S., and Hanson, B.E., *Nature*, 1989, **339**, 454.

64. For examples of uses of CPG beads see a) Marasco, C.J., Angelino, N.J., Paul, B. and Dolnick, B.J., *Tetrahedron Lett.*, 1994, **35**, 3029. b) Ruan, F., Yamamura, S., Hakomori, S-i. and Igarashi, Y., *Tetrahedron Lett.*, 1995, **36**, 6615.

65. a) Horváth, I.T., *Catal. Lett.*, 1990, **6**, 43. b) Gou, I., Hanson, B.E., Tóth, I., and Davis, M.E., *J. Organomet. Chem.*, 1991, **403**, 221. c) Gou, I., Hanson, B.E., Tóth, I., and Davis, M.E., *J. Mol. Catal.*, 1991, **70**, 363.

66. a) Frémy, G., Monflier, E., Carpentier, J-F., Castanet, Y., Mortreux, A., *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1474. b) Frémy, G., Monflier, E., Carpentier, J.F., Castanet, Y., Mortreux, A., *J. Catal.*, 1996, **162**, 339.

67. Fache, E., Mercier, C., Pagnier, N., Despeyroux, B., Panster, P., *J. Mol. Catal.*, 1993, **79**, 117.

68. a) Wan, K.T. and Davis, M.E., *Nature*, 1994, **370**, 449. b) Wan, K.T. and Davis, M.E., *J. Catal.*, 1994, **148**, 1. c) Wan, K.T. and Davis, M.E., *J. Catal.*, 1995, **152**, 25.

69. Anson, M.S., Leese, M.P., Tonks, L. and Williams, J.M.J., *J. Chem. Soc., Dalton Trans.*, 1998, 3529.

70. Both these reactions will be discussed in Chapter 2 and 3.

71. Arhancet, J.P., Davis, M.E., Merola, J.S., Hanson, B.E., *J. Catal.*, 1990, **121**, 327.

72. a) Arhancet, J.P., Davis, M.E. and Hanson, B.E., *J. Catal.*, 1991, **129**, 94; *ibid*, 1991, **129**, 100.

73. Yuan, Y., Xu, J., Zhang, H. and Tsai, K., *Catal. Lett.*, 1994, **29**, 387.

74. Tóth, I., Guo, I. and Hanson, B.E., *J. Mol. Catal. A: Chemical*, 1997, **116**, 217.

75. Naughton, M.J. and Drago, R.S., *J. Catal.*, 1995, **155**, 383.

76. Wan, K.T. and Davis, M.E., *J. Chem. Soc., Chem. Commun.*, 1993, 1262.

77. Wan, K.T. and Davis, M.E., *Tetrahedron: Asymmetry*, 1993, **4**, 2461.

78. Tóth, I., Hanson, B.E., Guo, I. and Davis, M.E., *Organometallics*, 1993, **12**, 848.

79. Smidt, G., Hafner, W., Jira, R., Sedlmeier, J., Sieber, R., Rültinger and Koger, H., *Angew. Chem.* 1959, **71**, 176.

80. Bäckvall, J.E., Åckermark, B. and Ljunggren, S.O., *J. Am. Chem. Soc.*, 1979, **107**, 2411.

81. Arhancet, J.P., Davis, M.E., Hanson, B.E., *Catal. Lett.*, 1991, **11**, 129.

82. Refer to Chapter 4 for applications of SAPC's as metal extractors.

83. a) Mizoroki, T., Mori, K. and Ozaki, A., *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581. b) Heck, R.F. and Nolley, J.P. Jr., *J. Org. Chem.*, 1972, **37**, 2320.

84. Dieck, H.A. and Heck, R.F., *J. Organomet. Chem.*, 1975, **93**, 259.

85. a) Heck, R.F., *Acc. Chem. Res.*, 1979, **12**, 146. b) Heck, R.F., *Org. React.*, 1982, **27**, 345. c) Heck, R.F., *Palladium Reagents in Organic Syntheses*, Academic Press, London, 1985. d) Tsuji, J., *Palladium Reagents and Catalysts - Innovations in Organic Synthesis*, Wiley, Chichester, 1995. e) de Meijere, A. and Meyer, F.E., *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379. f) Gibson, S.E. and Middleton, R.J., *Contemporary Organic Synthesis*, 1996, **3**, 447.

86. Nicolaou, K.C. and Sorensen, E.J., *Classics in Total Synthesis*, VCH, Weinheim, 1995.

87. Trost, B.M. and Murphy, D.J., *Organometallics*, 1985, **4**, 1143.

88. McCrindle, R., Ferguson, G., Arsenault, G.J. and McAlees, A.J., *J. Chem. Soc., Chem. Commun.*, 1983, 571 and references cited therein.

89. Amatore, C. Jutand, A. and M'Barki, M.A., *Organometallics*, 1985, **4**, 1143.

90. For the mechanism of the oxidative addition see a) Amatore, C. and Pflüger, F., *Organometallics*, 1990, **9**, 2276. b) Jutand, J. and Mosleh, A., *Organometallics*, 1995, **14**, 1810. c) Cianfriglia, P., Narducci, V., Sterzo, C.L., Viola, E., Bocelli, G. and Kodenkandath, T.A., *Organometallics*, 1996, **15**, 5220. d) Cabri, W and Candiani, I., *Acc. Chem. Res.*, 1995, **28**, 2.

91. Examples for *anti*-eliminations see Friestad, G.K. and Branchaud, B.P., *Tetrahedron Lett.*, 1995, **36**, 7047, and references cited therein.

92. Spencer, A., *J. Organomet. Chem.*, 1983, **258**, 101.

93. Hiroshige, M., Hauske, J.R. and Zhou, P., *Tetrahedron Lett.*, 1995, **36**, 4567.

94. Yu, K-L, Deshpande, M.S. and Vyas, D.M., *Tetrahedron Lett.*, 1994, **35**, 8919.

95. Andersson, C-M., Karabelas, K. and Hallberg, A., *J. Org. Chem.*, 1985, **50**, 3891.

96. Zhuangyu, Z., Yi, P., Honwen, H. and Tsi-Yu, K., *Synthesis*, 1991, 539.

97. Li, J., Mau, A.W-H. and Strauss, C.R., *J. Chem. Soc., Chem. Commun.*, 1997, 1275.

98. Choudary, B.M. and Sarma, M.R., *Tetrahedron Lett.*, 1990, **31**, 1495.

99. Jeffrey, T., *Tetrahedron Lett.*, 1994, **35**, 3051.

100. a) Lemaire-Audoire, S., Savignac, M., Dupuis, C. and Genêt, J.P., *Tetrahedron Lett.*, 1996, **37**, 2003. b) Casalnuovo, A.L. and Calabrese, J.C., *J. Am. Chem. Soc.*, 1990, **112**, 4324.

101. Genêt, J-P, Blart, E. and Savignac, M., *Synlett*, 1992, 715.

102. Kiji, J., Okano, T. and Hasegawa, T., *J. Mol. Catal. A* ,1995, **97**, 73.

103. Herd, O., Heβler, A., Hingst, M., Tepper, M. and Stelzer, O., *J. Organomet. Chem.*, 1996, **522**, 69.

104. Bumagin, N.A., More, P.G. and Beletskaya, I.P., *J. Organomet. Chem.*, 1989, **371**, 397.

105. a) Dibowski, H. and Schmidtchen, F.P., *Tetrahedron*, 1995, **51**, 2325. b) Hessler, A., Stelzer, O., Dibowski, H., Worm, K. and Schmidtchen, F.P., *J. Org. Chem.*, 1997, **62**, 2362.

106. The use of fewer equivalents of ligand afforded higher levels of leaching.

107. a) Mirza, A.R., Hellgardt, K., Williams, J.M.J., Thompson, D.F. and Tonks, L., *IChemE Jubilee*, 1997, 1217, Research Event, Nottingham. b) Mirza, A.R., Anson, M.S., Hellgardt, K., Leese, M.P., Thompson, D.F., Tonks, L. and Williams, J.M.J., *Organic Process Research & Development*, 1998, **2**, 325.

108. Bartik, T., Bartik, B., Hanson, B.E., Glass, T. and Bebout, W., *Inorg. Chem.*, 1992, **31**, 2667.

109. Herrmann, W.A., Albanese, G.P., Manetsberger, R.B., Lappe, P. and Bahrmann, H., *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 811.

110. Refer to Mirza, A.M. Thesis for a more detailed method.

111. Kiviaho, J., Hanaoka, T., Kubota, Y. and Sugi, Y., *J. Mol. Catal. A*, 1995, **101**, 25.

112. Terasawa, M., Kaneda, K., Imanaka, T. and Teranishi, S., *J. Organomet. Chem.*, 1978, **162**, 403.

113. dos Santos, S., Tong, Y., Quignard, F., Choplin, A., Sinou, D. and Dutasta, J.P., *Organometallics*, 1998, **17**, 78.

114. Yoshioka, N., Lahti, P.M., Kaneko, T., Kuzumaki, Y., Tsuchida, E. and Nishide, H., *J. Org. Chem.*, 1994, **59**, 4272.

115. Heck, R.F. and Melpolder, J.B., *J. Org. Chem.*, 1976, **41**, 265.

116. Chalk, A.J. and Magennis, S.A., *J. Org. Chem.*, 1976, **41**, 1206.

117. For examples of Heck reactions performed with beads **B** see Tonks, L., Anson, M.S., Hellgardt, K., Mirza, A.R., Thompson, D.F. and Williams, J.M.J., *Tetrahedron Lett.*, 1997, **38**, 4319.

118. Unpublished work of Plevyak, J.E.

119. Dickerson, J.E., Heck, R.F. and Plevyak, J.E., *J. Org. Chem.*, 1979, **44**, 4078.

120. Patel, B.A., Dickerson, J.E and Heck, R.F., *J. Org. Chem.*, 1978, **43**, 5018.

121. Tao, W., Nesbitt, S. and Heck, R.F., *J. Org. Chem.*, 1990, **55**, 63.

122. Lansky, A., Reiser, O. and de Meijere, A., *Synlett*, 1990, 405.

123. Voigt, K., Schink, U., Meyer, F.E. and de Meijere, A., *Synlett*, 1994, 189.

124. Ziegler, Jr. C.B. and Heck, R.F., *J. Org. Chem.*, 1978, **43**, 2941.

125. a) Frank, W.C., Kim, Y.C. and Heck, R.F., *J. Org. Chem.*, 1978, **43**, 2947. b) Ziegler, Jr. C.B. and Heck, R.F., *J. Org. Chem.*, 1978, **43**, 2949. c) Draper, T.L. and Bailey, T.R., *Synlett*, 1995, 157.

126. Bovy, P.R. and Rico, J.G., *Tetrahedron Lett.*, 1993, **34**, 8015.

127. Tsuji, J.,Takashashi, H. and Morikawa, M., *Tetrahedron Lett.*, 1965, 4387.

128. For examples of reviews on allylic substitutions see a) Frost, C.G., Howarth, J. and Williams, J.M.J., *Tetrahedron: Asymmetry*, 1992, **3**, 1089. b) Williams, J.M.J., *Synlett*, 1996, 705. c) Allen, J.V., Coote, S.J., Dawson, G.J., Frost, C.G., Martin, C.J. and Williams, J.M.J., *J. Chem. Soc., Perkin Trans 1*, 1994, 2065. d) Trost, B.M. and Van Vranken, D.L., *Chem. Rev.*, 1996, **96**, 395.

129. For examples of work pioneered in the group see a) Dawson, G.J., Frost, C.G., Williams, J.M.J., and Coote, S.J., *Tetrahedron Lett.*, 1993, **34**, 3149. b) Dawson, G.J., Williams, J.M.J. and Coote, S.J., *Tetrahedron Lett.*, 1995, **36**, 461. c) Dawson, G.J., Frost, C.G., Martin, C.J. and Williams, J.M.J., *Tetrahedron Lett.*, 1993, **34**, 7793. d) Frost, C.G. and Williams, J.M.J., *Tetrahedron: Asymmetry*, 1993, **4**, 1785. e) Allen, J.V., Bower, J.F. and Williams, J.M.J., *Tetrahedron: Asymmetry*, 1994, **5**, 1895. f) Allen, J.V., Dawson, G.J., Frost, C.G. and Williams, J.M.J., *Tetrahedron*, 1994, **50**, 799. g) Frost, C.G. and Williams, J.M.J., *Tetrahedron Lett.*, 1993, **34**, 2015.

130. Jumnah, R., Westwell, A.C. and Williams, J.M.J., *Synlett*, 1995, 821.

131. Bower, J.F. and Williams, J.M.J., *Synlett*, 1996, 685.

132. Tietze, L.F., Hippe, T. and Steinmetz, A., *J. Chem. Soc., Chem. Commun.*, 1998, 793.

133. Trost, B.M. and Keinan, E., *J. Am. Chem. Soc.*, 1978, 7779.

134. Bergbreiter, D.E. and Liu, Y-S., *Tetrahedron Lett.*, 1997, **38**, 7843.

135. Uozumi, Y., Danjo, H. and Hayashi, T., *Tetrahedron Lett.*, 1997, **38**, 3557.

136. Schneider, P., Quignard, F. and Choplin, A., *New. J. Chem.*, 1996, **20**, 545.

137. Choplin, A., Quignard, F., Leyrit, P., dos Santos, S., McGill, C., Graziani, O. and Sinou, D., *Supported reagents and catalysis in chemistry*, R.S.C, 1998, 150, and references cited therein.

138. Safi, M. and Sinou, D., *Tetrahedron Lett.*, 1991, **32**, 2025.

139. Blart, E., Genêt, J.P., Safi, M., Savignac, M., Sinou, D., *Tetrahedron*, 1994, **50**, 505.

140. Miyaura, N., Yanagi, T. and Suzuki, A., *Synth. Commun.*, 1981, **11**, 513.

141. For a review on Suzuki couplings see Miyaura, N. and Suzuki, A., *Chem. Rev.*, 1995, **95**, 2457.

142. Miyaura, N., Yamada, K. and Suzuki, A., *Tetrahedron lett.*, 1979, 3437.

143. Miyaura, N. and Suzuki, A., *J. Chem. Soc., Chem. Commun.*, 1979, 866.

144. Miyaura, N., Yano, T. and Suzuki, A., *Tetrahedron Lett.*, 1980, 2865.

145. Miyaura, N., Yamada, K., Suginome, H. and Suzuki, A., *J. Am. Chem. Soc.*, 1985, **107**, 972.

146. Moreno-Mañas, M., Pérez, M. and Pleixats, R., *J. Org. Chem.*, 1996, **61**, 2346.

147. Martin, A.R. and Yang, Y., *Acta. Chem. Scand.*, 1993, **47**, 221.

148. Backes, B.J. and Ellman, J.A., *J. Am. Chem. Soc.*, 1994, **116**, 11171.

149. Frenette, R. and Friesen, R.W., *Tetrahedron Lett.*, 1994, **35**, 9177.

150. Guiles, J.W., Johnson, S.G. and Murray, W.V., *J.Org. Chem.*, 1996, **61**, 5169.

151. Larhed, M., Lindeberg, G. and Hallberg, A., *Tetrahedron Lett.*, 1996, **37**, 8219.

152. Jang, S-B., *Tetrahedron Lett.*, 1997, **38**, 1793.

153. Fenger, I. and Le Drian, C., *Tetrahedron Lett.*, 1998, **39**, 4287.

154. a) Ishiyama, T., Miyaura, N. and Suzuki, A., *Chem. Lett.*, 1987, **1**, 25. b) Miyaura, N., Ishiyama, T., Sasaki, H., Ishikawa, M., Satoh, M. and Suzuki, A., *J. Am. Chem. Soc.*, 1989, **11**, 314.

155. Bumagin, N.A., Ponomaryov, A.B. and Beletskaya, I.P., *Synthesis*, 1984, 728.

156. Allen, J.V. and Williams, J.M.J., *Tetrahedron Lett.*, 1996, **37**, 1859.

157. Overman, L.E., *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 579.

158. Lutz, R.P, *Chem. Rev.*, 1984, **84**, 205.

159. a) Overman, L.E. and Campbell, C.B., *J. Org. Chem.*, 1976, **41**, 3338. b) Overman, L.E., Campbell, C.B. and Knoll, F.M., *J. Am. Chem. Soc*, 1978, **100**, 4822.

160. Overman, L.E. and Knoll, F.M., *Tetrahedron Lett.*, 1979, 321.

161. Meyer, K., *Chem. Abstr.*, 1976, **84**, 89 629s.

162. Calter, M., Hollis, K., Overman, L.E., Ziller, J. and Zipp, G.G., *J. Org. Chem.*, 1997, **62**, 1449.

163. Overman, L.E. and Zipp, G.G., *J. Org. Chem.*, 1997, **62**, 2288.

164. a) Tamaru, Y., Yoshida, Z., Yamada, Y., Mukai, K. and Yoshioka, Z., *J. Org. Chem.*, 1983, **48**, 1293. b) Yamada, Y., Mukai, K., Yoshioka, Z., Tamaru, Y., Yoshida, Z., *Tetrahedron Lett.*, 1979, 5015.

165. a) Trost, B.M., Runge, T.A., *J. Am. Chem. Soc.*, 1981, **103**, 7559. b) Trost, B.M. and Keinan, E., *J. Org. Chem.*, 1979, **44**, 3451.

166. Thanks to Matt Clarke for kindly supplying the sodium salt of cyanoacetic acid ligand.

167. This work was performed prior to the synthesis of the three water-soluble nitrile ligands.

168. Dartt, C.B. and Davis, M.E., *Ind. Eng. Chem. Res.*, 1994, **33**, 2887.

169. a) Clark, J.H. and Macquarrie, D.J., *J. Chem. Soc., Chem. Commun.*, 1998, 853. b) Clark, J.H., Cullen, S.R., Barlow, S.J. and Bastock, T.W., *J. Chem. Soc., Perkin Trans 2*, 1994, 1117. c) Clark, J.H., Butterworth, A.J., Taverner, S.J., Teasdale, A.J., Barlow, S.J., Bastock, T.W. and Martin, K., *J. Chem. Tech. Biotechnol.*, 1997, **68**, 367.

170. Macquarrie, D.J., *Tetrahedron Lett.*, 1998, **39**, 4125.

171. Sheldon, R. A., *J. Chem. Tech. Biotechnol.*, 1997, **68**, 381.

172. Feng, X., Frywell, G.E., Wang, L.-Q., Kim, A.Y., Liu, J. and Kemner, K.M., *Science*, 1997, **276**, 923.

173. Sinner, F., Buchmeiser, M.R., Tessadri, R., Mupa, M., Wurst, K. and Bonn, G.K., *J. Am. Chem. Soc.*, 1998, **120**, 2790.

174. Available from Degussa Limited, Winterton House, Winterton Way, Macclesfield, Cheshire, SK11 OLP, U.K.

175. Kakoi, T., Horinouchi, N., Goto, M. and Nakashio, F., *J. Membrane Sci.*, 1996, **118**, 63.

176. Guyon, V. and Guy, A., *Tetrahedron*, 1995, **51**, 4065.

177. Davisil beads were found to be just as effective at extracting palladium as the previously used CPG beads.

178. **All** tests on palladium content involve removal of any solvent *in vacuo* and subsequent extraction of palladium. Follow methods described in experimental for palladium determination.

179. All dilution factors were taken into account when evaluating palladium measurements.

180. All literature melting points are quoted from the Aldrich catalogue, 1998.

181. Grehn, L. and Ragnarsson, U., *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 510.

182. Somei, M., Saida, Y. and Komura, N., *Chem. Pharm. Bull.*, 1986, **34**, 4116.

183. Kikukawa, K., Naritomi, M., He, G-X., Wada, F. and Matsuda, T., *J. Org. Chem.*, 1985, **50**, 299.

184. Cook, J.W. and Lawrence, C.A., *J. Chem. Soc.*, 1938, 58.

185. Hartley, F.R., Murray, S.G. and McAuliffe, C.A., *Inorg. Chem.*, 1979, **18**, 1394.

APPENDIX

Calculation 1. Typical calculation for Palladium leaching levels in the final product

For example, atomic absorption result for Pd analysis = 1 ppm

The amount of Pd in the product (mg) = $\frac{\text{ppm (mg/ml) x 3 (sample in 3ml water)}}{\text{1000 (ml)}}$

$$= \frac{1 \times 3}{1000}$$

$$= \mathbf{0.003\ mg}$$

Assuming we used palladium chloride (22.1 mg) as catalyst in the bead preparation. The maximum amount palladium (0) in the reaction could be calculated as follows:

$PdCl_2$ = 177.31 RMM

Pd (0) = 106.4 RAM

Hence amount Pd (0) on $PdCl_2 = \frac{106.4}{177.31}$

$$= 0.60\ \text{Pd (0)}$$

Pd (0) in $PdCl_2$ = 0.60 x 22.1 mg

= **13.3 mg** maximum of Pd (0) in reaction that could leach

Hence, total amount of Pd (0) in solution (%) after performing a bead reaction

$$= \frac{\text{total amount of Pd (0) in product (mg)}}{\text{maximum amount of Pd (0) that could leach (mg)}} \times 100$$

$$= \frac{0.003\ \text{mg}}{13.3\ \text{mg}} \times 100$$

= ***0.02%*** of maximal amount of palladium (0) that could potentially leach into product.

Results are quoted in mg and % terms, i.e. for this example minimal palladium leaching is found in the sample (<0.01 mg, <0.1%).

Molecular model 1. Suspected structure of Pd-ligand complex ($PdCl_2$-TPPTS)

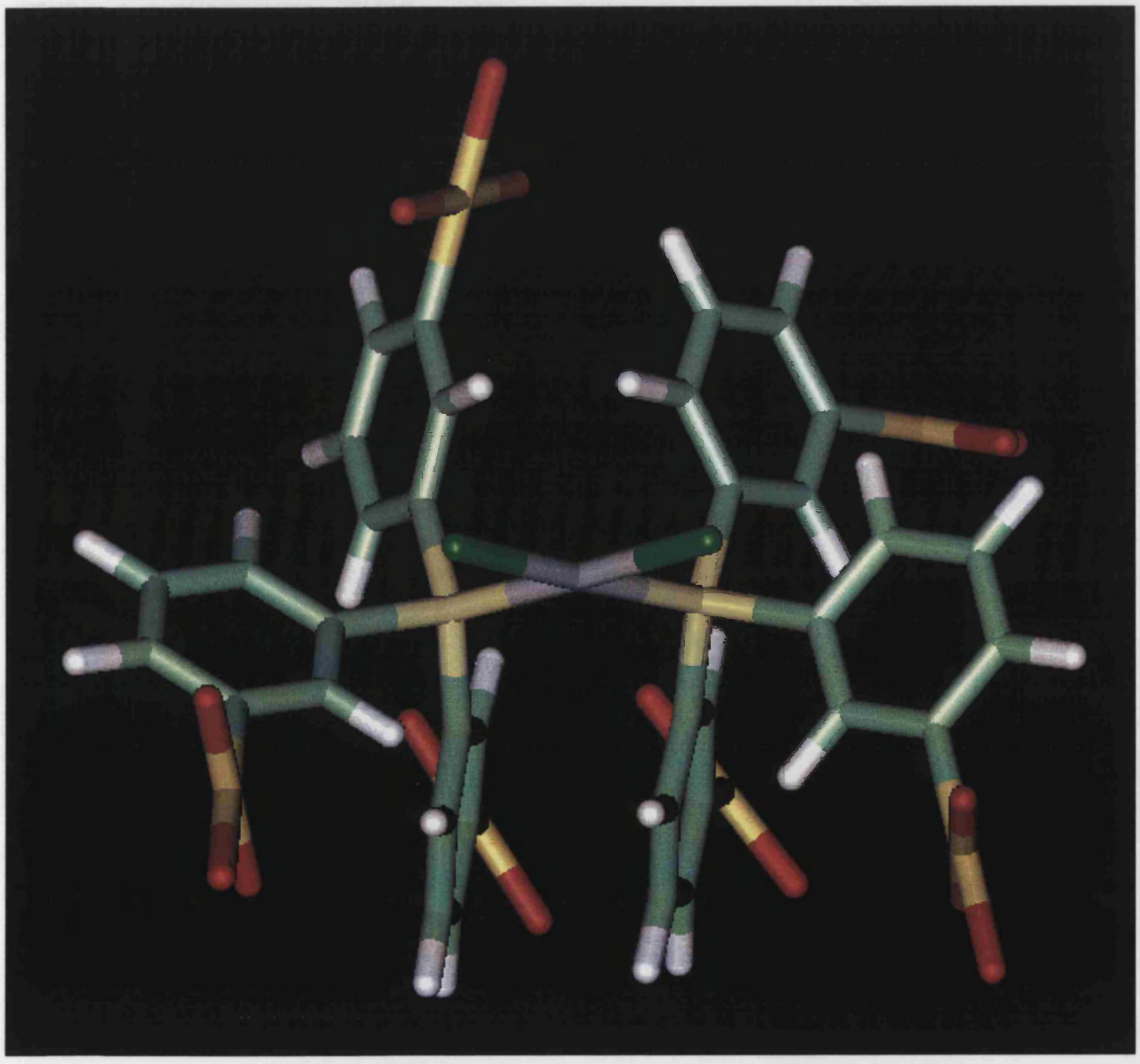


Diagram 1. "Filter technique" subsequent to the Heck reaction

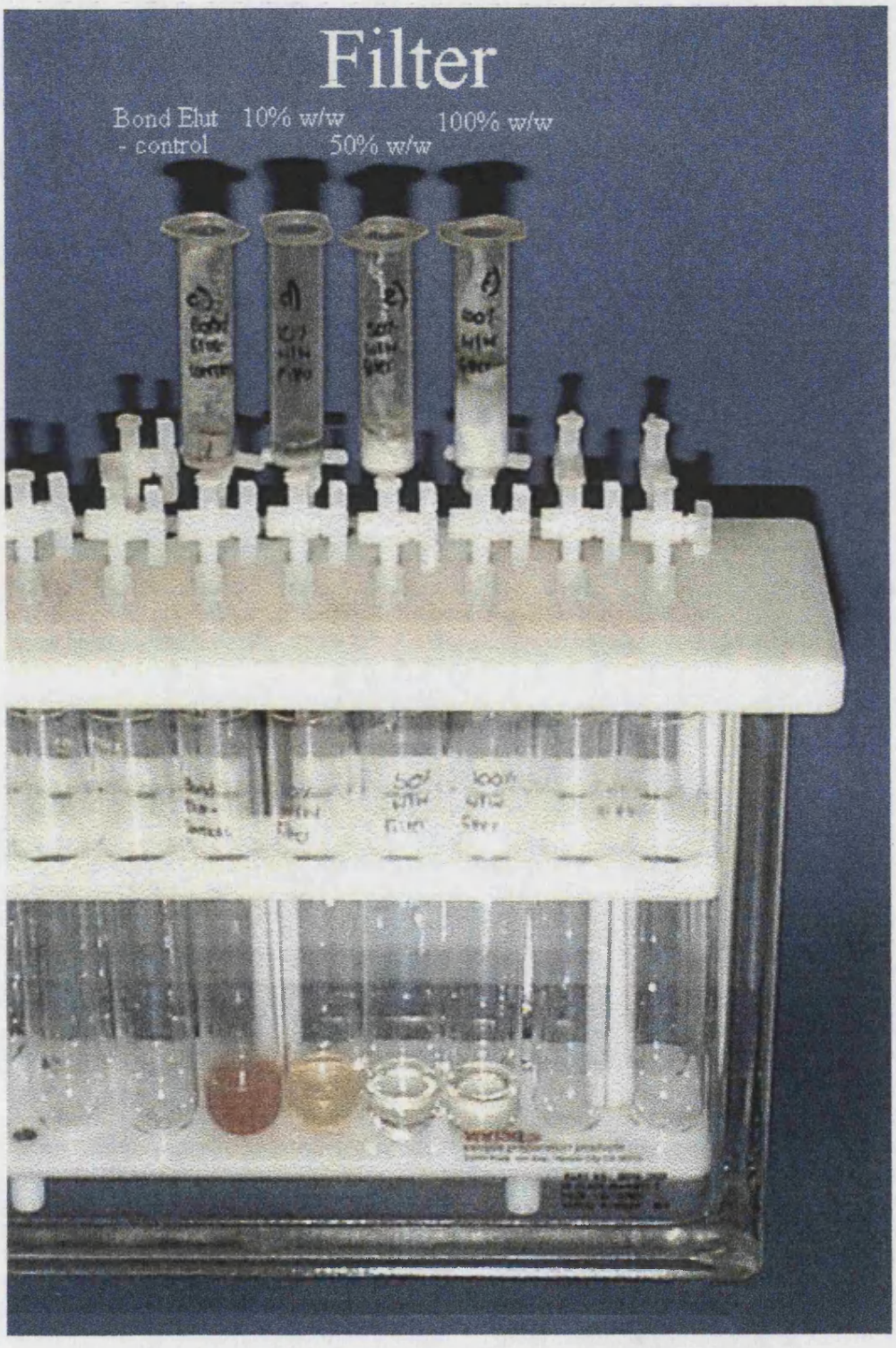
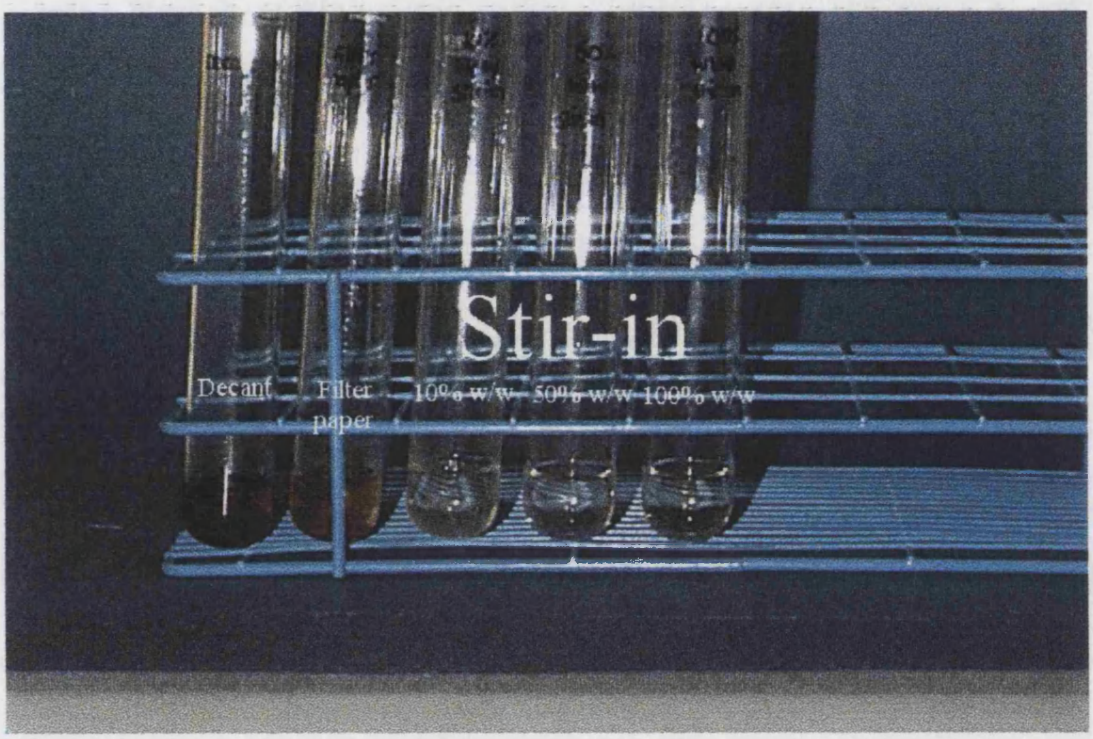


Diagram 2. "Stir-in technique" subsequent to the Heck reaction



Graph 1. Filter preparation optimisation

Filter solution - TPPTS : $Pd(OAc)_2$